

Ivermectin for COVID-19: real-time meta analysis of 88 studies

Covid Analysis, Jun 24, 2022, Version 195

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Together Trial: impossible data, blinding failure, randomization failure, data pledge violation, protocol violati...

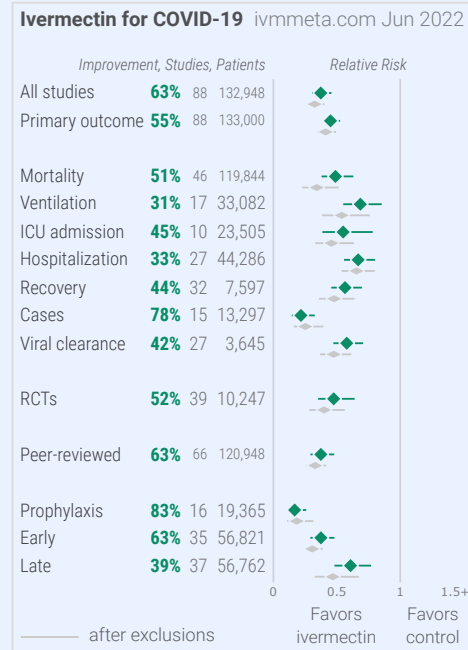
Responses: [ACTIV-6](#), [Popp](#), [GidMK](#), [Scott Alexander](#), [BBC](#), [Strongyloides](#), [Angkasekwinai](#)

- Statistically significant improvements are seen for mortality, ventilation, ICU admission, hospitalization, recovery, cases, and viral clearance. All remain significant after exclusions. 56 studies from 51 independent teams in 22 different countries show statistically significant improvements in isolation (39 primary outcome, 36 most serious outcome).

- Meta analysis using the most serious outcome shows 63% [52-71%] and 83% [74-89%] improvement for early treatment and prophylaxis, with similar results after exclusion based sensitivity analysis, for primary outcomes, for peer-reviewed studies, and for RCTs.

- Results are very robust – in worst case exclusion sensitivity analysis 55 of 88 studies must be excluded to avoid finding statistically significant efficacy.

- While many treatments have some level of efficacy, they do not replace vaccines and other measures to avoid infection. Only 23% of ivermectin studies show zero events in the treatment arm. Multiple treatments are typically used in combination, which may be significantly more effective.
- No treatment, vaccine, or intervention is 100% available and effective for all variants. All practical, effective, and safe means should be used. Denying the efficacy of treatments increases mortality, morbidity, collateral damage, and endemic risk.
- Over 20 countries have adopted ivermectin for COVID-19. The evidence base is much larger and has much lower conflict of interest than typically used to approve drugs.
- All data to reproduce this paper and sources are in the [appendix](#). See [\[Bryant, Hariyanto, Kory, Lawrie, Nardelli\]](#) for other meta analyses with similar results confirming efficacy.



Evidence base used for other COVID-19 approvals

Medication	Studies	Patients	Improvement
Molnupiravir (UK)	1	775	50%
Budesonide (UK)	1	1,779	17%
Remdesivir (USA EUA)	1	1,063	31%

Casirivimab/i.. (USA EUA)	1	799	66%
<i>Ivermectin evidence</i>	88	132,948	63% [54-70%]

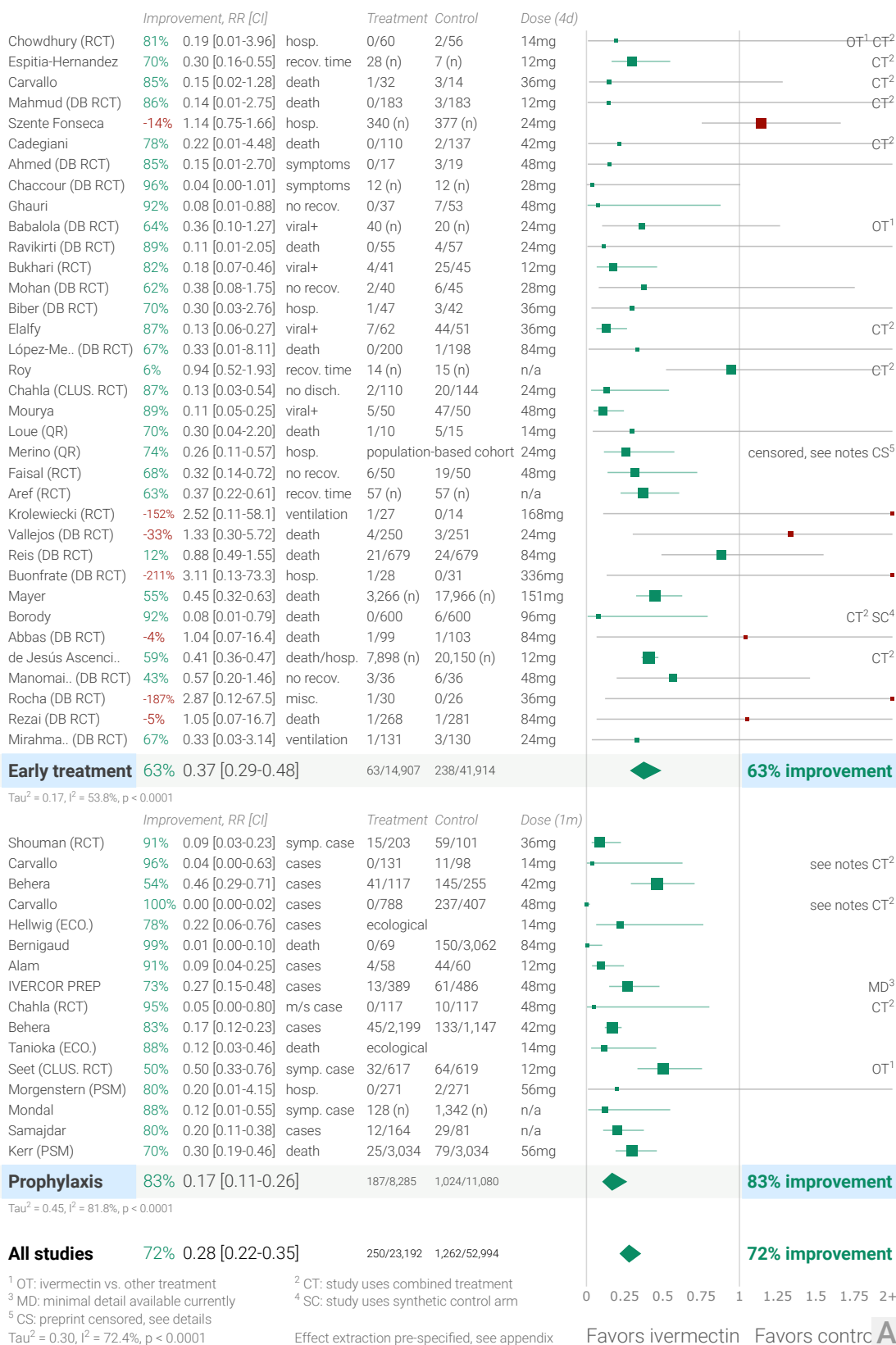
HIGHLIGHTS

Ivermectin reduces risk for COVID-19 with very high confidence for mortality, ventilation, ICU admission, hospitalization, progression, recovery, cases, viral clearance, and in pooled analysis.

We show traditional outcome specific analyses and combined evidence from all studies, incorporating treatment delay, a primary confounding factor in COVID-19 studies.

Real-time updates and corrections, transparent analysis with all results in the same format, consistent protocol for 42 treatments.

Ivermectin COVID-19 early treatment and prophylaxis studies ivmmeta.com Jun 2022



to chance with an ineffective treatment (the probability of $\geq k$ heads in n coin tosses, or the one-sided sign test / binomial test). Analysis of publication bias is important and adjustments may be needed if there is a bias toward publishing positive results.

Figure 2 shows stages of possible treatment for COVID-19. **Prophylaxis** refers to regularly taking medication before becoming sick, in order to prevent or minimize infection. **Early Treatment** refers to treatment immediately or soon after symptoms appear, while **Late Treatment** refers to more delayed treatment.

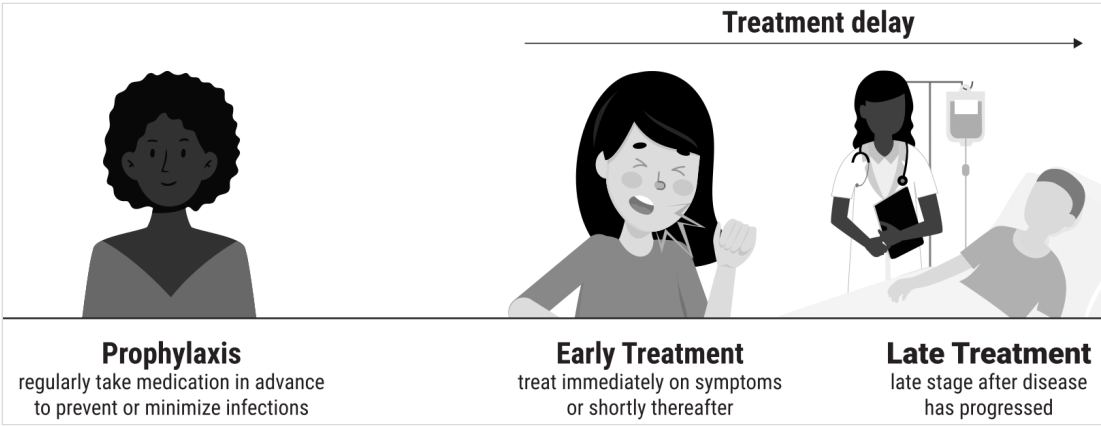


Figure 2. Treatment stages.

Preclinical Research

18 *In Silico* studies support the efficacy of ivermectin [Alvarado, Aminpour, Bello, Choudhury, Eweas, Francés-Monerris, Francés-Monerris (B), González-Paz, González-Paz (B), Kern, Muthusamy, Parvez, Qureshi, Rana, Saha, Schöning, Swargiary, Udofia].

12 *In Vitro* studies support the efficacy of ivermectin [Caly, Delandre, Jeffreys, Jitobaom, Jitobaom (B), Li, Liu, Mody, Mountain Valley MD, Segatori, Surnar, Yesilbag].

7 *In Vivo* animal studies support the efficacy of ivermectin [Albariqi, Arévalo, Chaccour, de Melo, Errecalde, Madrid, Zheng].

5 studies investigate novel formulations of ivermectin that may be more effective for COVID-19 [Albariqi, Albariqi (B), Chaccour, Errecalde, Mansour].

Preclinical research is an important part of the development of treatments, however results may be very different in clinical trials. Preclinical results are not used in this paper.

Results

Figure 3 shows a visual overview of the results. Figure 4, 5, and 6 show results by treatment stage. Figure 7, 8, 9, 10, 11, 12, 13, and 14 show forest plots for a random effects meta-analysis of all studies with pooled effects, and for studies reporting mortality results, ICU admission, mechanical ventilation, hospitalization, recovery, COVID-19 cases, and viral clearance results only. Figure 15 shows results for peer reviewed trials only, and the [supplementary data](#) contains peer reviewed and individual outcome results after exclusions. Table 1 and Table 2 summarize the results.

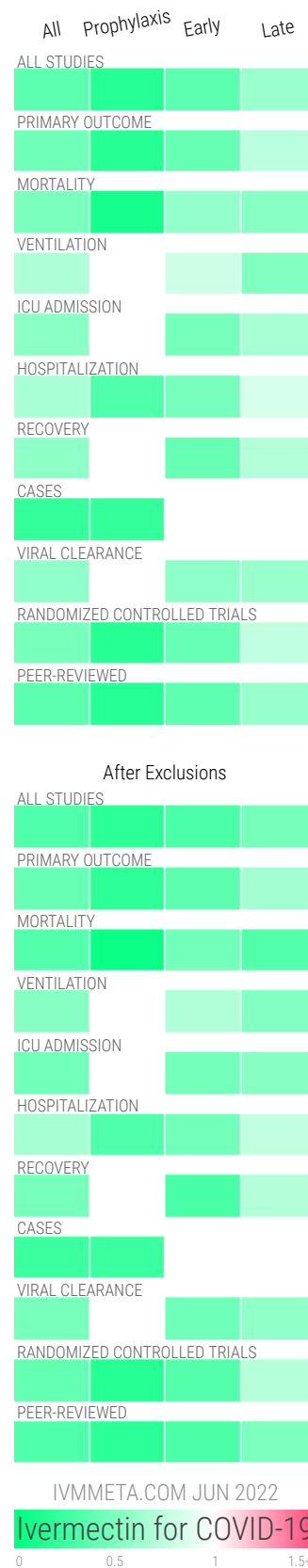


Figure 3. Overview of results.

Treatment time	Number of studies reporting positive effects	Total number of studies	Percentage of studies reporting positive effects	Probability of an equal or greater percentage of positive results from an ineffective treatment	Random effects meta-analysis results
Early treatment	28	35	80.0%	1 in 4 thousand	63% improvement RR 0.37 [0.29-0.48] p < 0.0001
Late treatment	30	37	81.1%	1 in 10 thousand	39% improvement RR 0.61 [0.48-0.77] p < 0.0001
Prophylaxis	16	16	100%	1 in 66 thousand	83% improvement RR 0.17 [0.11-0.26] p < 0.0001
All studies	74	88	84.1%	1 in 39 billion	63% improvement RR 0.37 [0.30-0.46] p < 0.0001

Table 1. Results by treatment stage.

	Studies	Prophylaxis	Early treatment	Late treatment	Patients
All studies	88	83% [74-89%]	63% [52-71%]	39% [23-52%]	132,948
Peer-reviewed	66	83% [73-90%]	62% [50-71%]	40% [18-56%]	120,948
After exclusions	59	82% [68-89%]	69% [61-76%]	53% [33-68%]	116,941
Randomized Controlled Trials	39	84% [25-96%]	58% [42-70%]	24% [3-40%]	10,247
RCTs after exclusions	31	84% [25-96%]	66% [54-75%]	29% [4-47%]	6,967

Table 2. Results by treatment stage for all studies and with different exclusions.

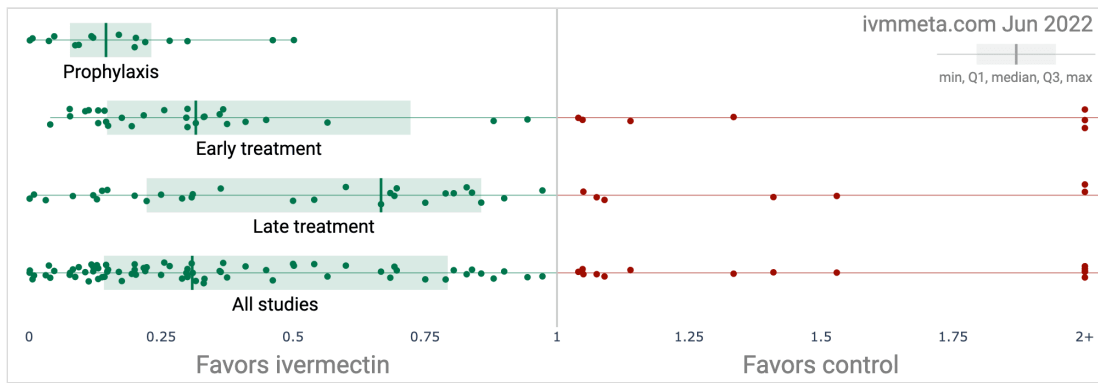


Figure 4. Results by treatment stage.

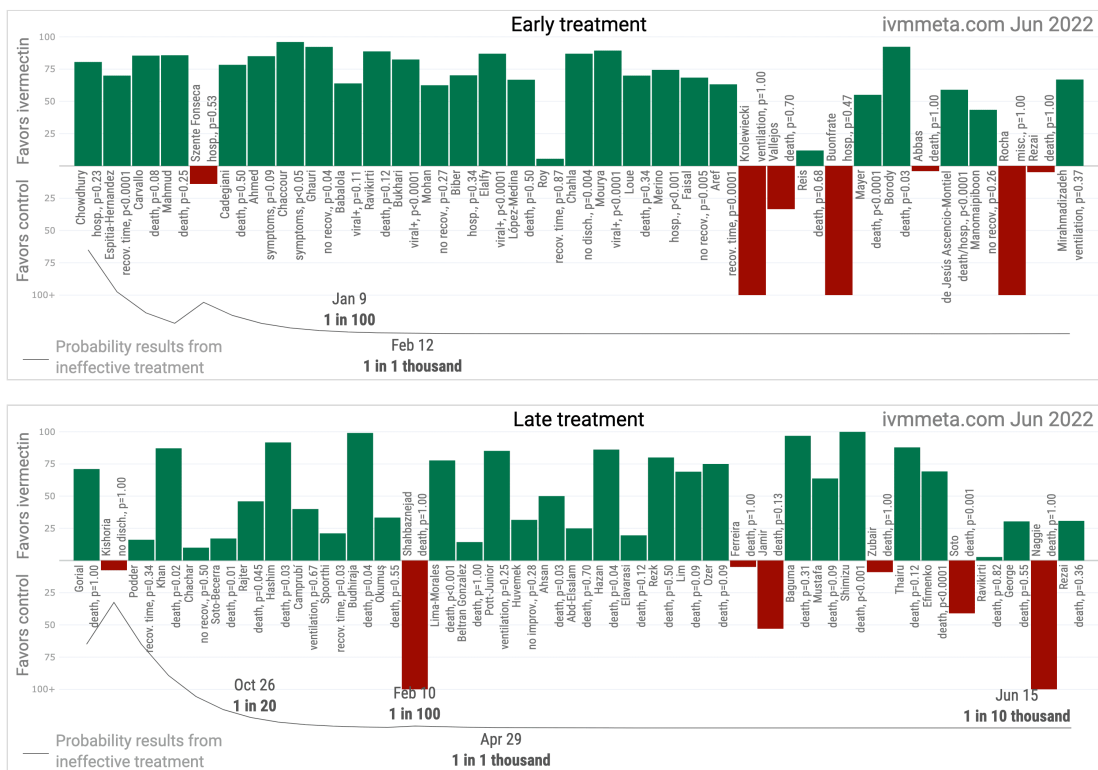


Figure 5. Chronological history of early and late treatment results, with the probability that the observed or greater frequency of positive results were generated by an ineffective treatment.

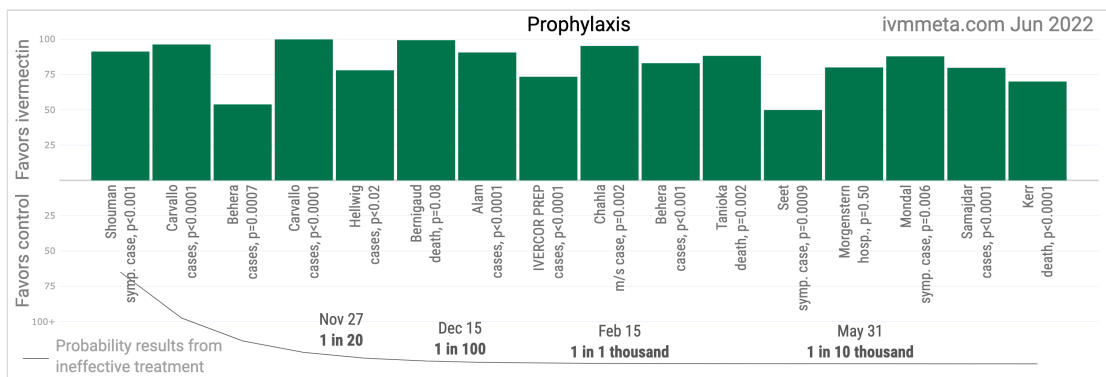


Figure 6. Chronological history of prophylaxis results.

All 88 ivermectin COVID-19 studies

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	Improvement, RR [CI]	Treatment	Control	Dose (4d)	
Chowdhury (RCT)	81% 0.19 [0.01-3.96]	hosp.	0/60 2/56	14mg	OT ¹ CT ²
Espitia-Hernandez	70% 0.30 [0.16-0.55]	recov. time	28 (n) 7 (n)	12mg	CT ²
Carvallo	85% 0.15 [0.02-1.28]	death	1/32 3/14	36mg	CT ²
Mahmud (DB RCT)	86% 0.14 [0.01-2.75]	death	0/183 3/183	12mg	CT ²
Szente Fonseca	-14% 1.14 [0.75-1.66]	hosp.	340 (n) 377 (n)	24mg	
Cadegiani	78% 0.22 [0.01-4.48]	death	0/110 2/137	42mg	CT ²
Ahmed (DB RCT)	85% 0.15 [0.01-2.70]	symptoms	0/17 3/19	48mg	
Chaccour (DB RCT)	96% 0.04 [0.00-1.01]	symptoms	12 (n) 12 (n)	28mg	
Ghuri	92% 0.08 [0.01-0.88]	no recov.	0/37 7/53	48mg	
Babalola (DB RCT)	64% 0.36 [0.10-1.27]	viral+	40 (n) 20 (n)	24mg	OT ¹
Ravikirti (DB RCT)	89% 0.11 [0.01-2.05]	death	0/55 4/57	24mg	
Bukhari (RCT)	82% 0.18 [0.07-0.46]	viral+	4/41 25/45	12mg	
Mohan (DB RCT)	62% 0.38 [0.08-1.75]	no recov.	2/40 6/45	28mg	
Biber (DB RCT)	70% 0.30 [0.03-2.76]	hosp.	1/47 3/42	36mg	
Elalfy	87% 0.13 [0.06-0.27]	viral+	7/62 44/51	36mg	CT ²
López-Me.. (DB RCT)	67% 0.33 [0.01-8.11]	death	0/200 1/198	84mg	
Roy	6% 0.94 [0.52-1.93]	recov. time	14 (n) 15 (n)	n/a	CT ²
Chahla (CLUS. RCT)	87% 0.13 [0.03-0.54]	no disch.	2/110 20/144	24mg	
Mourya	89% 0.11 [0.05-0.25]	viral+	5/50 47/50	48mg	
Loue (QR)	70% 0.30 [0.04-2.20]	death	1/10 5/15	14mg	
Merino (QR)	74% 0.26 [0.11-0.57]	hosp.	population-based cohort	24mg	censored, see notes CS ⁵
Faisal (RCT)	68% 0.32 [0.14-0.72]	no recov.	6/50 19/50	48mg	
Aref (RCT)	63% 0.37 [0.22-0.61]	recov. time	57 (n) 57 (n)	n/a	
Krolewiecki (RCT)	-152% 2.52 [0.11-58.1]	ventilation	1/27 0/14	168mg	
Vallejos (DB RCT)	-33% 1.33 [0.30-5.72]	death	4/250 3/251	24mg	
Reis (DB RCT)	12% 0.88 [0.49-1.55]	death	21/679 24/679	84mg	
Buonfrate (DB RCT)	-211% 3.11 [0.13-73.3]	hosp.	1/28 0/31	336mg	
Mayer	55% 0.45 [0.32-0.63]	death	3,266 (n) 17,966 (n)	151mg	
Borody	92% 0.08 [0.01-0.79]	death	0/600 6/600	96mg	CT ² SC ⁴
Abbas (DB RCT)	-4% 1.04 [0.07-16.4]	death	1/99 1/103	84mg	
de Jesús Ascenci..	59% 0.41 [0.36-0.47]	death/hosp.	7,898 (n) 20,150 (n)	12mg	CT ²
Manomai.. (DB RCT)	43% 0.57 [0.20-1.46]	no recov.	3/36 6/36	48mg	
Rocha (DB RCT)	-187% 2.87 [0.12-67.5]	misc.	1/30 0/26	36mg	
Rezai (DB RCT)	-5% 1.05 [0.07-16.7]	death	1/268 1/281	84mg	
Mirahma.. (DB RCT)	67% 0.33 [0.03-3.14]	ventilation	1/131 3/130	24mg	

Early treatment 63% 0.37 [0.29-0.48] 63/14,907 238/41,914 **63% improvement**

Tau² = 0.17, I² = 53.8%, p < 0.0001

	Improvement, RR [CI]	Treatment	Control	Dose (4d)	
Gorial	71% 0.29 [0.01-5.76]	death	0/16 2/71	14mg	
Kishoria (RCT)	-8% 1.08 [0.57-2.02]	no disch.	11/19 7/13	12mg	
Podder (RCT)	16% 0.84 [0.55-1.12]	recov. time	32 (n) 30 (n)	14mg	
Khan	87% 0.13 [0.02-1.00]	death	1/115 9/133	12mg	
Chachar (RCT)	10% 0.90 [0.44-1.83]	no recov.	9/25 10/25	36mg	
Soto-Becerra	17% 0.83 [0.71-0.97]	death	92/203 1,438/2,630	14mg	
Rajter (PSM)	46% 0.54 [0.27-0.99]	death	13/98 24/98	14mg	
Hashim (SB RCT)	92% 0.08 [0.00-1.44]	death	0/59 6/70	28mg	CT ²
Camprubi	40% 0.60 [0.18-2.01]	ventilation	3/13 5/13	14mg	
Spoorthi	21% 0.79 [0.64-0.98]	recov. time	50 (n) 50 (n)	n/a	CT ²
Budhiraja	99% 0.01 [0.00-0.15]	death	0/34 103/942	n/a	
Okumuş (DB RCT)	33% 0.67 [0.27-1.64]	death	6/30 9/30	56mg	
Shahbazn.. (DB RCT)	-197% 2.97 [0.13-70.5]	death	1/35 0/34	14mg	
Lima-Morales	78% 0.22 [0.12-0.41]	death	15/481 52/287	12mg	CT ²
Beltran .. (DB RCT)	14% 0.86 [0.29-2.56]	death	5/36 6/37	12mg	
Pott-Junior (RCT)	85% 0.15 [0.01-1.93]	ventilation	1/27 1/4	14mg	censored, see notes
Huvmek (DB RCT)	32% 0.68 [0.38-1.23]	no improv.	13/50 19/50	84mg	
Ahsan	50% 0.50 [0.28-0.90]	death	17/110 17/55	21mg	CT ²
Abd-El salam (RCT)	25% 0.75 [0.17-3.06]	death	3/82 4/82	36mg	
Hazan	86% 0.14 [0.01-2.15]	death	0/24 synthetic	24mg	CT ² SC ⁴
Elavarasi	20% 0.80 [0.61-1.06]	death	48/283 311/1,475	n/a	
Rezk	80% 0.20 [0.01-4.13]	death	0/160 2/160	72mg	
Lim (RCT)	69% 0.31 [0.09-1.11]	death	3/241 10/249	112mg	
Ozer	75% 0.25 [0.06-1.13]	death	2/60 8/60	28mg	
Ferreira	-5% 1.05 [0.32-3.43]	death	3/21 11/81	n/a	
Jamir (ICU)	-53% 1.53 [0.88-2.67]	death	32/76 69/190	n/a	CU-patients
Baguma	97% 0.03 [0.00-11.7]	death	7 (n) 474 (n)	n/a	
Mustafa	64% 0.36 [0.12-1.14]	death	3/73 42/371	varies	
Shimizu	100% 0.00 [0.00-0.01]	death	0/39 8/49	14mg	
Zubair	-9% 1.09 [0.33-3.64]	death	5/90 5/98	12mg	



Figure 7. Random effects meta-analysis for all studies. This plot shows pooled effects, analysis for individual outcomes is below, and more details on pooled effects can be found in the heterogeneity section. Effect extraction is pre-specified, using the most serious outcome reported. Simplified dosages are shown for comparison, these are the total dose in the first four days for treatment, and the monthly dose for prophylaxis, for a 70kg person. For details of effect extraction and full dosage information see the appendix.

All 46 ivermectin COVID-19 mortality results

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Figure 8. Random effects meta-analysis for mortality.

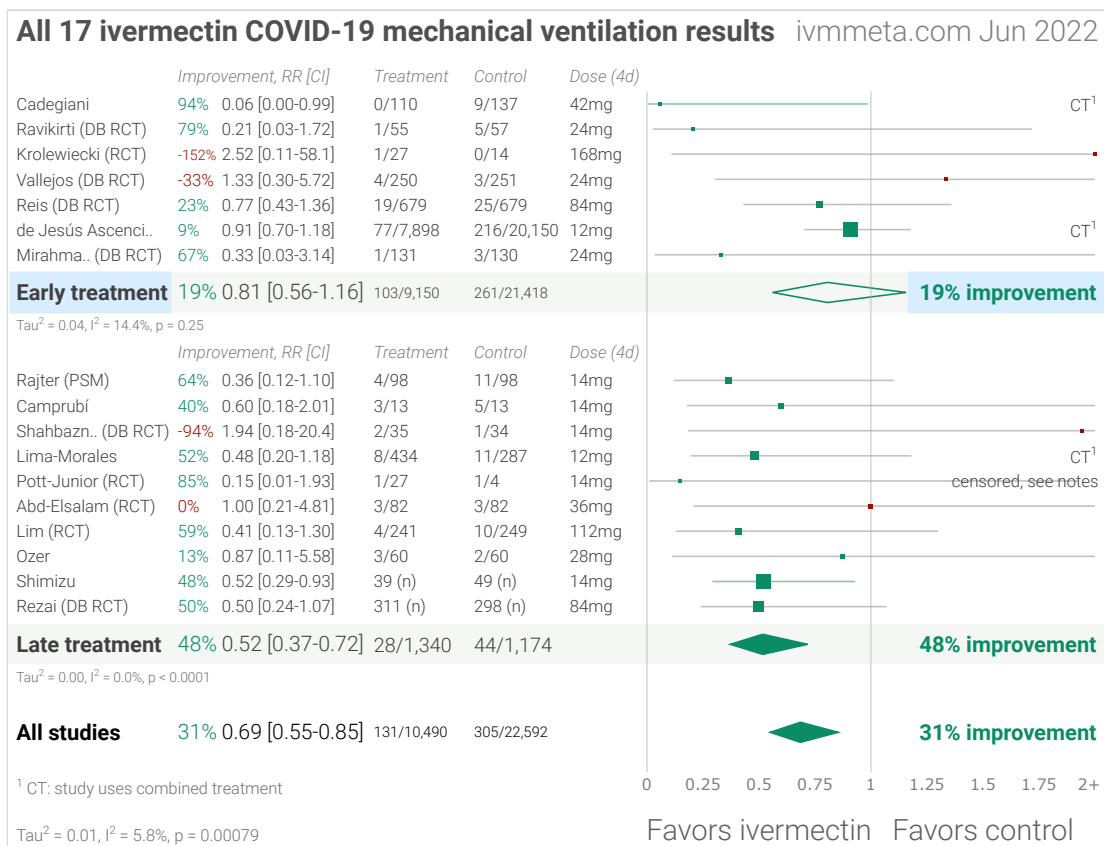


Figure 9. Random effects meta-analysis for mechanical ventilation.

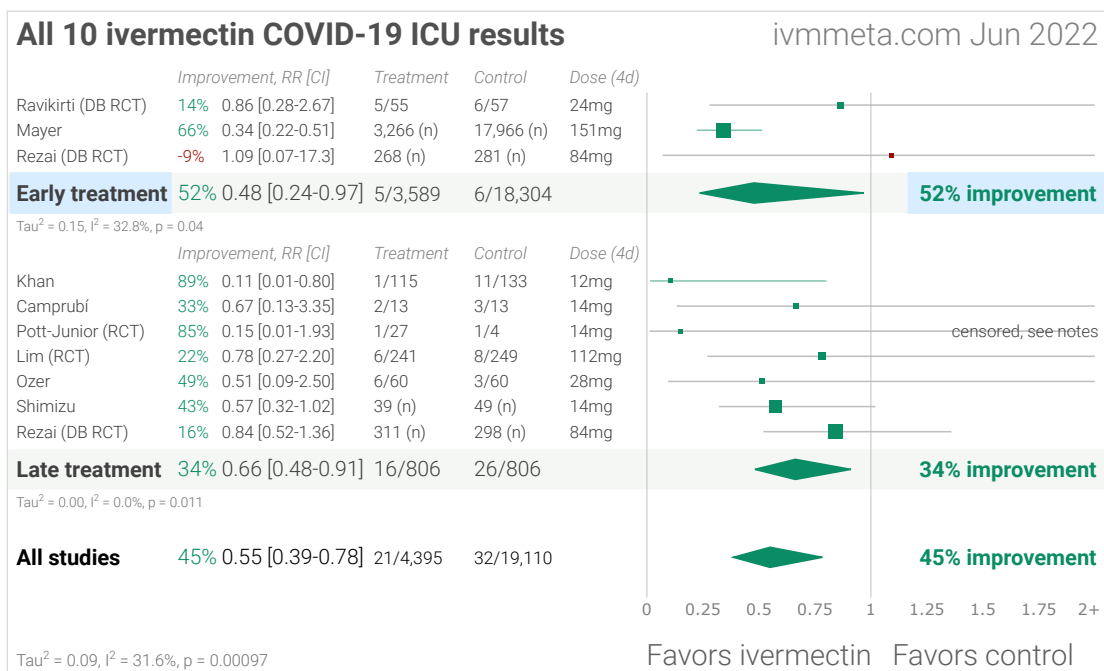


Figure 10. Random effects meta-analysis for ICU admission.

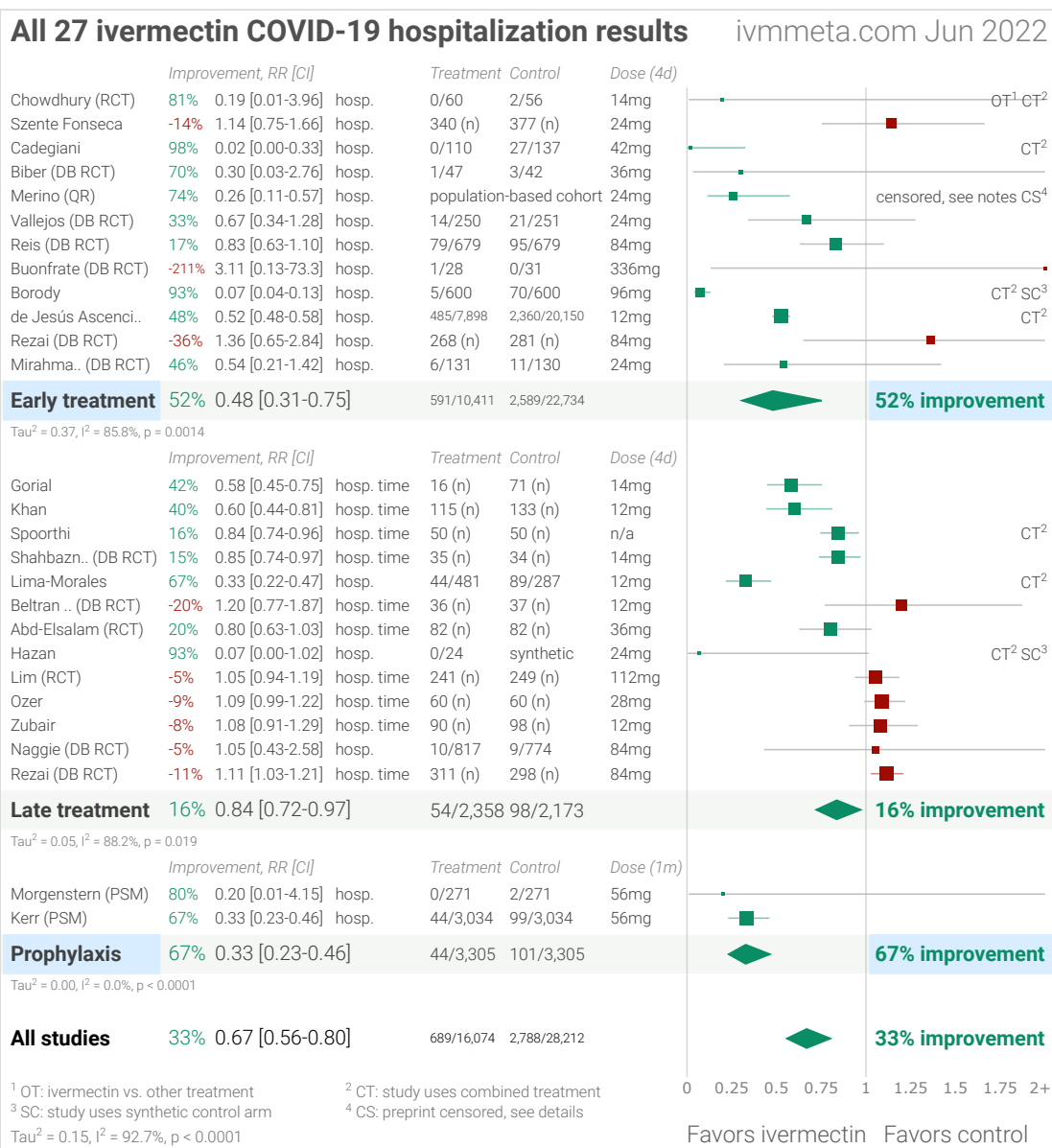


Figure 11. Random effects meta-analysis for hospitalization.

All 32 ivermectin COVID-19 recovery results

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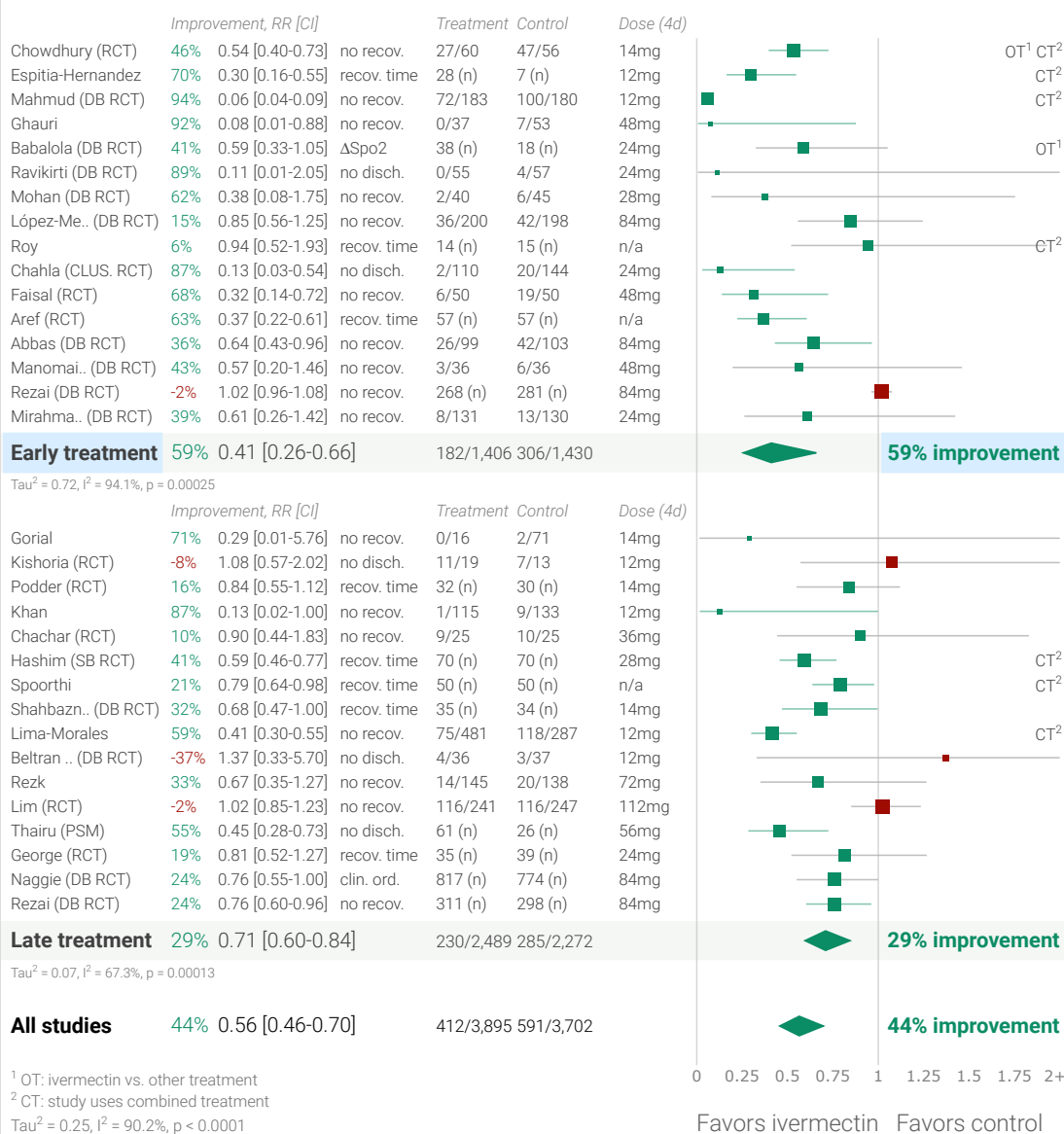


Figure 12. Random effects meta-analysis for recovery results only.

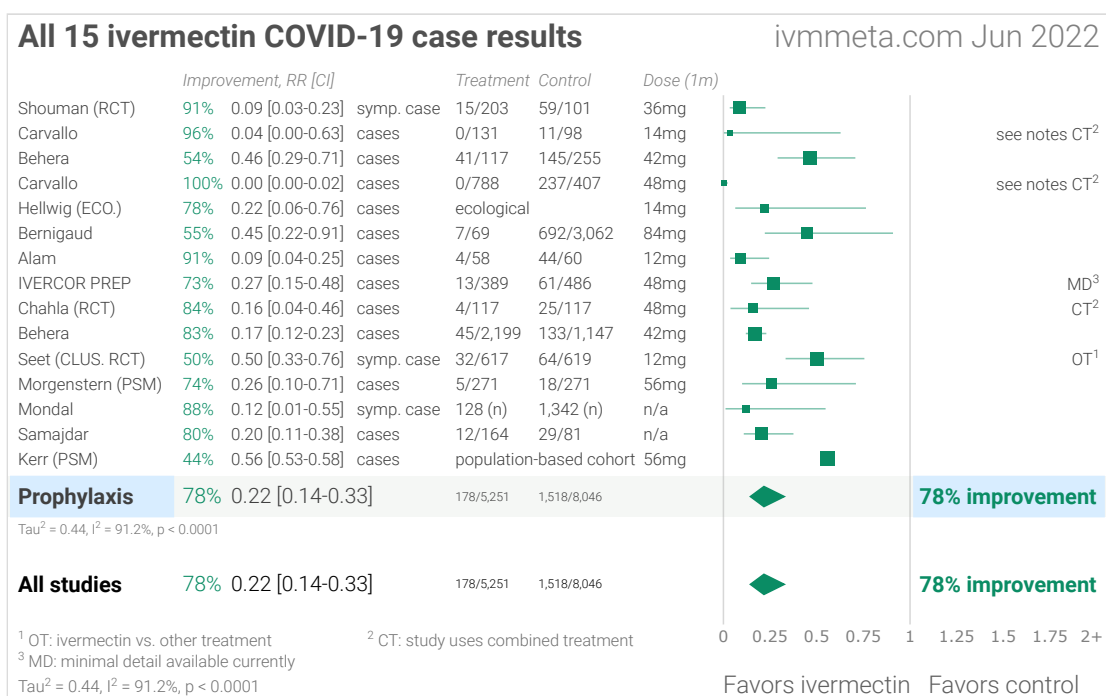


Figure 13. Random effects meta-analysis for COVID-19 case results.

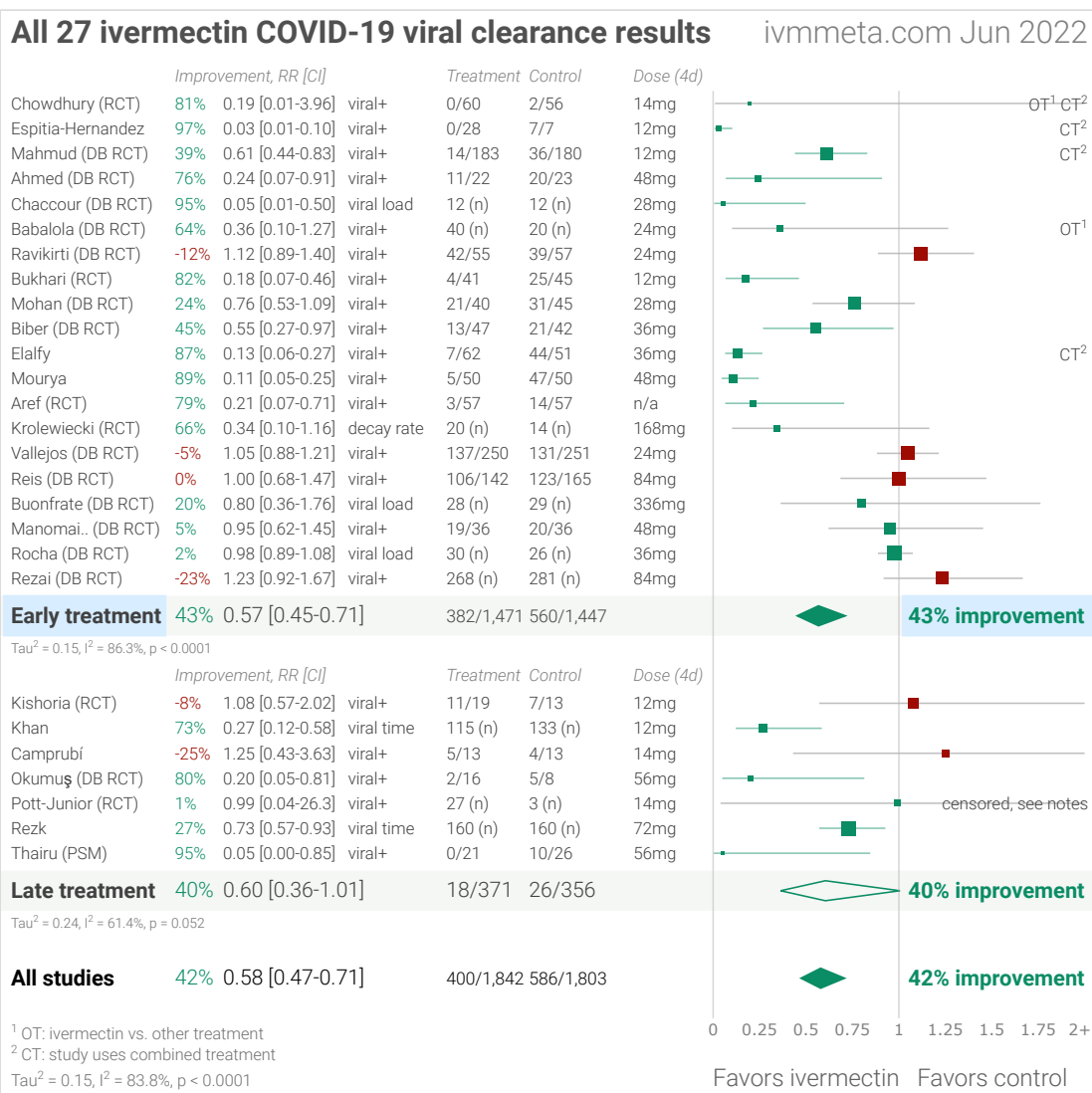


Figure 14. Random effects meta-analysis for viral clearance.

All 66 ivermectin COVID-19 peer reviewed trials

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	Improvement, RR [CI]	Treatment	Control	Dose (4d)		
Chowdhury (RCT)	81% 0.19 [0.01-3.96]	hosp.	0/60	2/56	14mg	OT ¹ CT ²
Espitia-Hernandez	70% 0.30 [0.16-0.55]	recov. time	28 (n)	7 (n)	12mg	CT ²
Carvallo	85% 0.15 [0.02-1.28]	death	1/32	3/14	36mg	CT ²
Mahmud (DB RCT)	86% 0.14 [0.01-2.75]	death	0/183	3/183	12mg	CT ²
Szente Fonseca	-14% 1.14 [0.75-1.66]	hosp.	340 (n)	377 (n)	24mg	
Cadegiani	78% 0.22 [0.01-4.48]	death	0/110	2/137	42mg	CT ²
Ahmed (DB RCT)	85% 0.15 [0.01-2.70]	symptoms	0/17	3/19	48mg	
Chaccour (DB RCT)	96% 0.04 [0.00-1.01]	symptoms	12 (n)	12 (n)	28mg	
Ghuri	92% 0.08 [0.01-0.88]	no recov.	0/37	7/53	48mg	
Babalola (DB RCT)	64% 0.36 [0.10-1.27]	viral+	40 (n)	20 (n)	24mg	OT ¹
Ravikirti (DB RCT)	89% 0.11 [0.01-2.05]	death	0/55	4/57	24mg	
Mohan (DB RCT)	62% 0.38 [0.08-1.75]	no recov.	2/40	6/45	28mg	
Elalfy	87% 0.13 [0.06-0.27]	viral+	7/62	44/51	36mg	CT ²
López-Me.. (DB RCT)	67% 0.33 [0.01-8.11]	death	0/200	1/198	84mg	
Mourya	89% 0.11 [0.05-0.25]	viral+	5/50	47/50	48mg	
Loue (QR)	70% 0.30 [0.04-2.20]	death	1/10	5/15	14mg	
Faisal (RCT)	68% 0.32 [0.14-0.72]	no recov.	6/50	19/50	48mg	
Aref (RCT)	63% 0.37 [0.22-0.61]	recov. time	57 (n)	57 (n)	n/a	
Krolewiecki (RCT)	-152% 2.52 [0.11-58.1]	ventilation	1/27	0/14	168mg	
Vallejos (DB RCT)	-33% 1.33 [0.30-5.72]	death	4/250	3/251	24mg	
Reis (DB RCT)	12% 0.88 [0.49-1.55]	death	21/679	24/679	84mg	
Buonfrate (DB RCT)	-211% 3.11 [0.13-73.3]	hosp.	1/28	0/31	336mg	
Mayer	55% 0.45 [0.32-0.63]	death	3,266 (n)	17,966 (n)	151mg	
Abbas (DB RCT)	-4% 1.04 [0.07-16.4]	death	1/99	1/103	84mg	
de Jesús Ascenci..	59% 0.41 [0.36-0.47]	death/hosp.	7,898 (n)	20,150 (n)	12mg	CT ²
Rezai (DB RCT)	-5% 1.05 [0.07-16.7]	death	1/268	1/281	84mg	
Mirahma.. (DB RCT)	67% 0.33 [0.03-3.14]	ventilation	1/131	3/130	24mg	
Early treatment	62% 0.38 [0.29-0.50]		52/14,029	178/41,006		62% improvement

Tau² = 0.16, I² = 54.0%, p < 0.0001

	Improvement, RR [CI]	Treatment	Control	Dose (4d)		
Kishoria (RCT)	-8% 1.08 [0.57-2.02]	no disch.	11/19	7/13	12mg	
Podder (RCT)	16% 0.84 [0.55-1.12]	recov. time	32 (n)	30 (n)	14mg	
Chachar (RCT)	10% 0.90 [0.44-1.83]	no recov.	9/25	10/25	36mg	
Rajter (PSM)	46% 0.54 [0.27-0.99]	death	13/98	24/98	14mg	
Hashim (SB RCT)	92% 0.08 [0.00-1.44]	death	0/59	6/70	28mg	CT ²
Camprubi	40% 0.60 [0.18-2.01]	ventilation	3/13	5/13	14mg	
Spoorthi	21% 0.79 [0.64-0.98]	recov. time	50 (n)	50 (n)	n/a	CT ²
Okumus (DB RCT)	33% 0.67 [0.27-1.64]	death	6/30	9/30	56mg	
Shahbazn.. (DB RCT)	-197% 2.97 [0.13-70.5]	death	1/35	0/34	14mg	
Lima-Morales	78% 0.22 [0.12-0.41]	death	15/481	52/287	12mg	CT ²
Beltran .. (DB RCT)	14% 0.86 [0.29-2.56]	death	5/36	6/37	12mg	
Pott-Junior (RCT)	85% 0.15 [0.01-1.93]	ventilation	1/27	1/4	14mg	censored, see notes
Ahsan	50% 0.50 [0.28-0.90]	death	17/110	17/55	21mg	CT ²
Abd-Elsalam (RCT)	25% 0.75 [0.17-3.06]	death	3/82	4/82	36mg	
Rezk	80% 0.20 [0.01-4.13]	death	0/160	2/160	72mg	
Lim (RCT)	69% 0.31 [0.09-1.11]	death	3/241	10/249	112mg	
Ozer	75% 0.25 [0.06-1.13]	death	2/60	8/60	28mg	
Ferreira	-5% 1.05 [0.32-3.43]	death	3/21	11/81	n/a	
Jamir (ICU)	-53% 1.53 [0.88-2.67]	death	32/76	69/190	n/a	CU patients
Mustafa	64% 0.36 [0.12-1.14]	death	3/73	42/371	varies	
Shimizu	100% 0.00 [0.00-0.01]	death	0/39	8/49	14mg	
Zubair	-9% 1.09 [0.33-3.64]	death	5/90	5/98	12mg	
Efimenko (PSM)	69% 0.31 [0.20-0.48]	death	1,072 (n)	40,536 (n)	n/a	self-censored, see notes OT ¹
Soto	-41% 1.41 [1.16-1.76]	death	280/484	374/934	n/a	
George (RCT)	30% 0.70 [0.25-1.93]	death	5/35	8/39	24mg	
Rezai (DB RCT)	31% 0.69 [0.35-1.39]	death	13/311	18/298	84mg	
Late treatment	40% 0.60 [0.44-0.82]		430/3,759	696/43,893		40% improvement

Tau² = 0.38, I² = 83.5%, p = 0.0014

	Improvement, RR [CI]	Treatment	Control	Dose (1m)		
Shouman (RCT)	91% 0.09 [0.03-0.23]	symp. case	15/203	59/101	36mg	
Behera	54% 0.46 [0.29-0.71]	cases	41/117	145/255	42mg	
Carvallo	100% 0.00 [0.00-0.02]	cases	0/788	237/407	48mg	see notes CT ²
Hellwig (ECO.)	78% 0.22 [0.06-0.76]	cases	ecological		14mg	
Bernigaud	99% 0.01 [0.00-0.10]	death	0/69	150/3,062	84mg	
Alam	91% 0.09 [0.04-0.25]	cases	4/58	44/60	12mg	
Chahla (RCT)	95% 0.05 [0.00-0.80]	m/s case	0/117	10/117	48mg	CT ²
Behera	83% 0.17 [0.12-0.23]	cases	45/2,199	133/1,147	42mg	

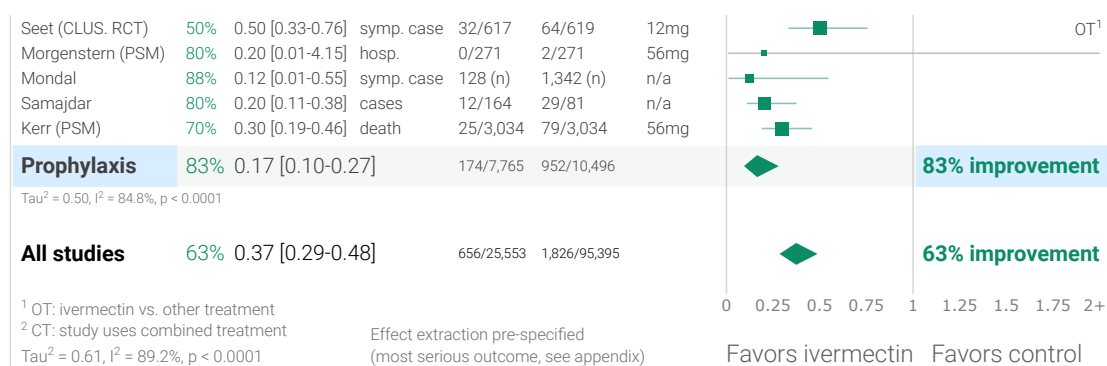


Figure 15. Random effects meta-analysis for peer-reviewed trials. [Zeraatkar] analyze 356 COVID-19 trials, finding no significant evidence that peer-reviewed studies are more trustworthy. They also show extremely slow review times during a pandemic. Authors recommend using preprint evidence, with appropriate checks for potential falsified data, which provides higher certainty much earlier. Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details.

Randomized Controlled Trials (RCTs)

Results restricted to Randomized Controlled Trials (RCTs) are shown in Figure 16, 17, 18, 19, and 20, and Table 3. The [supplementary data](#) contains RCT results after exclusions.

RCTs help to make study groups more similar, however they are subject to many biases, including age bias, treatment delay bias, severity of illness bias, regulation bias, recruitment bias, trial design bias, followup time bias, selective reporting bias, fraud bias, hidden agenda bias, vested interest bias, publication bias, and publication delay bias [Jadad], all of which have been observed with COVID-19 RCTs.

RCTs have a bias against finding an effect for interventions that are widely available — patients that believe they need the intervention are more likely to decline participation and take the intervention. This is illustrated with the extreme example of an RCT showing no significant differences for use of a parachute when jumping from a plane [Yeh]. RCTs for ivermectin are more likely to enroll low-risk participants that do not need treatment to recover, making the results less applicable to clinical practice. This bias is likely to be greater for widely known treatments such as ivermectin. The bias may also be greater in locations where ivermectin is more easily obtained. Note that this bias does not apply to the typical pharmaceutical trial of a new drug that is otherwise unavailable.

Evidence shows that non-RCT trials can also provide reliable results. [Concato] find that well-designed observational studies do not systematically overestimate the magnitude of the effects of treatment compared to RCTs. [Anglemyer] summarized reviews comparing RCTs to observational studies and found little evidence for significant differences in effect estimates. [Lee] shows that only 14% of the guidelines of the Infectious Diseases Society of America were based on RCTs. Evaluation of studies relies on an understanding of the study and potential biases. Limitations in an RCT can outweigh the benefits, for example excessive dosages, excessive treatment delays, or Internet survey bias could have a greater effect on results. Ethical issues may also prevent running RCTs for known effective treatments. For more on issues with RCTs see [Deaton, Nichol].

In summary, we need to evaluate each trial on its own merits. RCTs for a given medication and disease may be more reliable, however they may also be less reliable. For example, consider trials for an off-patent medication, very high conflict of interest trials may be more likely to be RCTs (and more likely to be

large trials that dominate meta analyses).

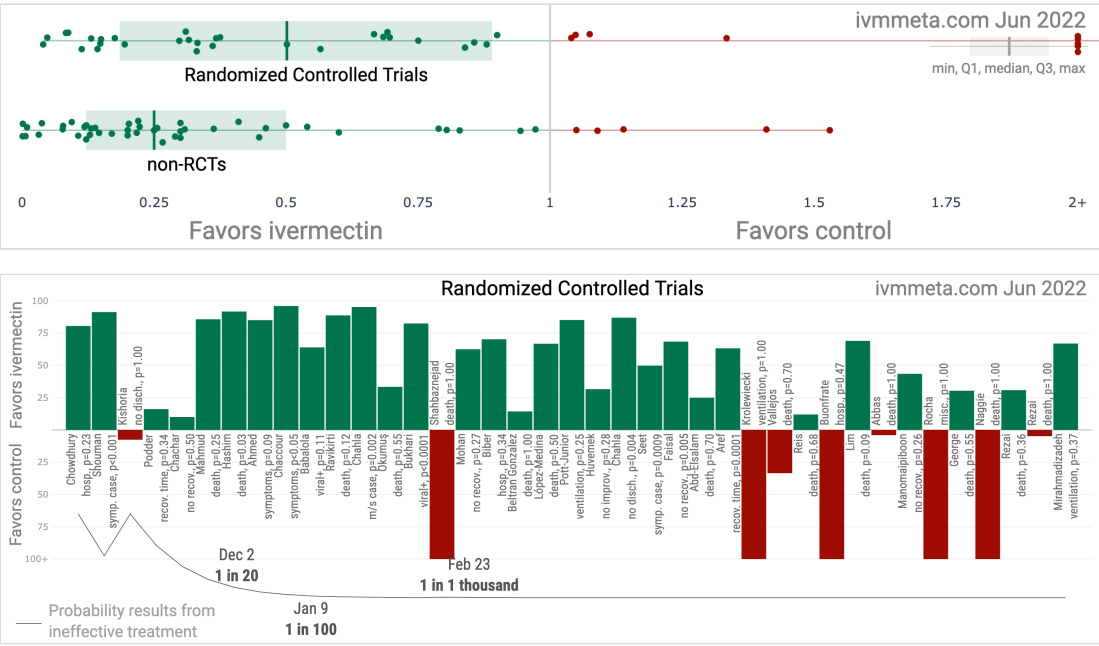


Figure 16. Randomized Controlled Trials. The distribution of results for RCTs is similar to the distribution for all other studies.

All 39 ivermectin COVID-19 Randomized Controlled Trials

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Figure 17. Random effects meta-analysis for Randomized Controlled Trials only. Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details.

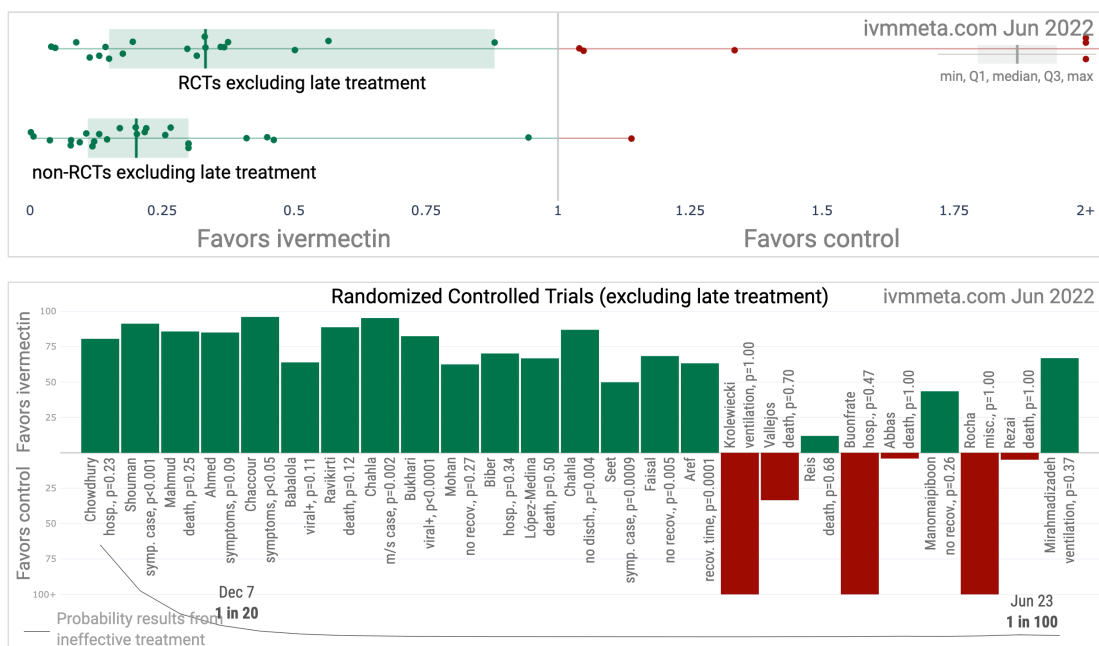


Figure 18. RCTs excluding late treatment.

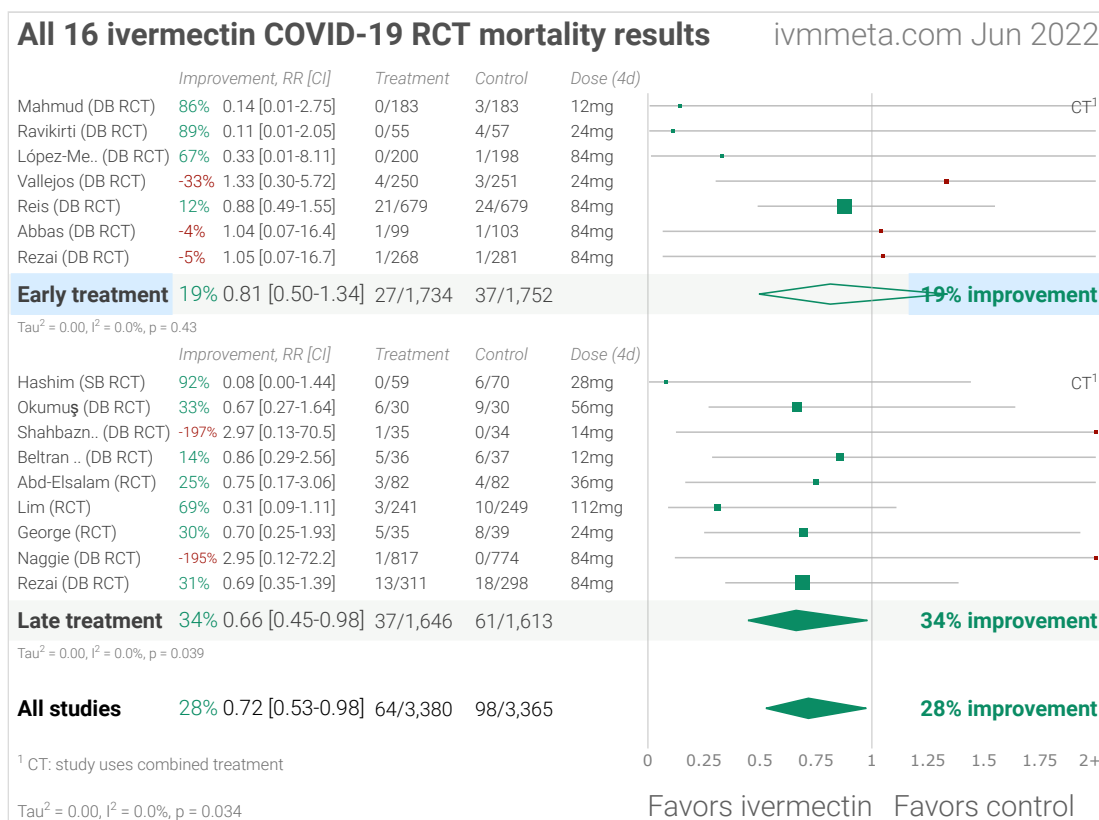


Figure 19. Random effects meta-analysis for RCT mortality results.

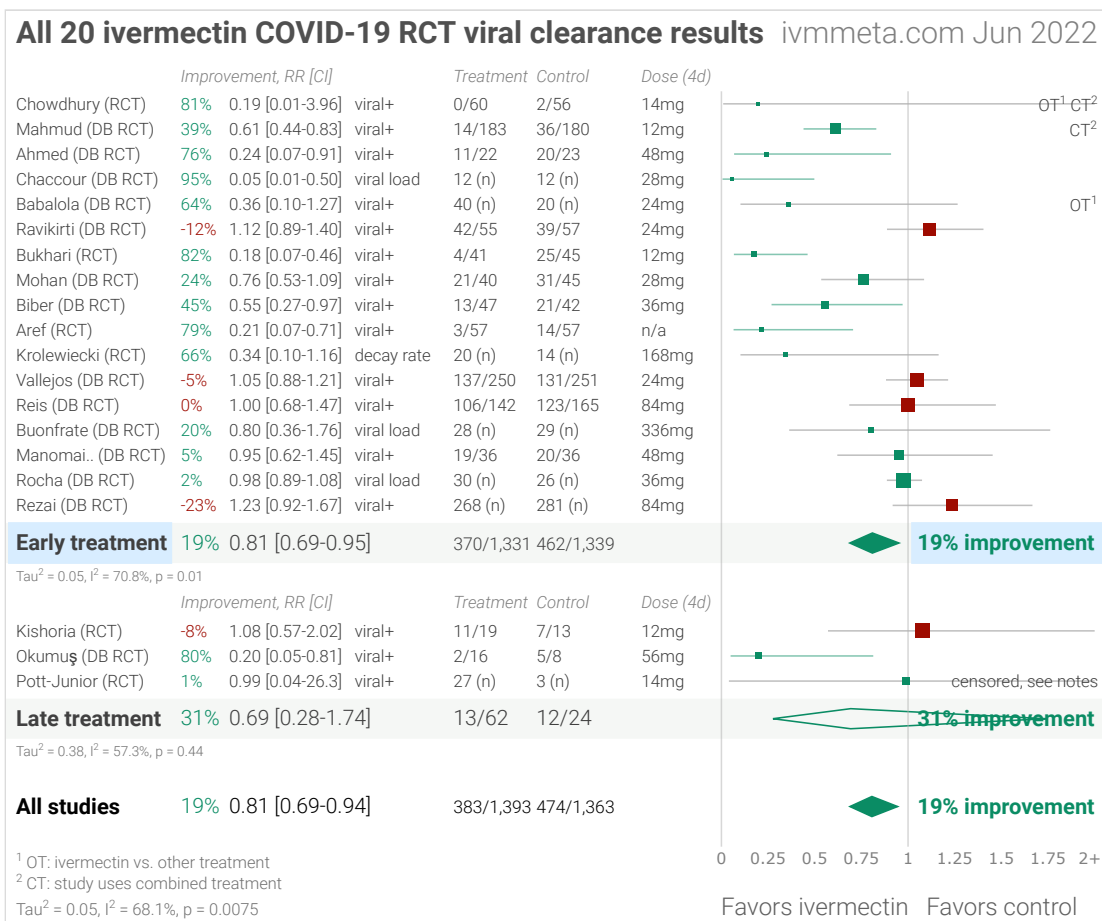


Figure 20. Random effects meta-analysis for RCT viral clearance results.

Treatment time	Number of studies reporting positive effects	Total number of studies	Percentage of studies reporting positive effects	Probability of an equal or greater percentage of positive results from an ineffective treatment	Random effects meta-analysis results
Randomized Controlled Trials	30	39	76.9%	1 in 2 thousand	52% improvement RR 0.48 [0.35-0.64] p < 0.0001
Randomized Controlled Trials (excluding late treatment)	19	25	76.0%	1 in 137	65% improvement RR 0.35 [0.23-0.53] p < 0.0001

Table 3. Summary of RCT results.

Exclusions

To avoid bias in the selection of studies, we analyze all non-retracted studies. Here we show the results after excluding studies with critical issues likely to alter results, non-standard studies, and studies where very minimal detail is currently available. Our bias evaluation is based on analysis of each study and identifying when there is a significant chance that limitations will substantially change the outcome of the study. We believe this can be more valuable than checklist-based approaches such as Cochrane GRADE, which may underemphasize serious issues not captured in the checklists, overemphasize issues unlikely to alter outcomes in specific cases (for example, lack of blinding for an objective mortality outcome, or certain specifics of randomization with a very large effect size), or be subject to bias. However, they can also be very high quality [\[Bryant\]](#).

A team of researchers has analyzed the data in ivermectin studies and identified several studies with concerns. Retracted studies are not in this analysis. All other studies that the team has identified are excluded here. For more details see the [response](#) section.

Detailed description of issues with [\[López-Medina\]](#) can be found in the [study notes](#) section.

[\[Soto-Becerra\]](#) is a database analysis covering anyone with ICD-10 COVID-19 codes, which includes asymptomatic PCR+ patients. Therefore many patients in the control group are likely asymptomatic with regards to SARS-CoV-2, but in the hospital for another reason. For those that had symptomatic COVID-19, there is also likely significant confounding by indication. KM curves show that the treatment groups were in more serious condition, with more than the total excess mortality at 30 days occurring on day 1. All treatments are worse than the control group at 30 days, while at the latest followup all treatments show lower mortality than control. The machine learning system used also appears over-parameterized and likely to result in significant overfitting and inaccurate results. There is also no real control group in this study - patients receiving the treatments after 48 hours were put in the control group. Authors also state that outcomes within 24 hours were excluded, however the KM curves show significant mortality at day 1 (only for the treatment groups). Several protocol violations have also been reported in this study [\[Yim\]](#). Note that this study provides both 30 day mortality and weighted KM curves up to day 43 for ivermectin, we use the day 43 results as per our protocol. [\[IVERCOR PREP\]](#) reports prophylaxis results, however only very minimal details are currently available in a news report. [\[Hellwig\]](#) analyze African countries and COVID-19 cases in October 2020 as a function of whether widespread prophylactic use of ivermectin is used for parasitic infections. [\[Tanioka\]](#) perform a similar analysis for COVID-19 mortality in January 2021. These studies are excluded because they are not clinical trials. [\[Shahbaznejad\]](#) had only one death that occurred in a patient that was critically ill at the time of admission and died within the first 24 hours. [\[Galan\]](#) perform an RCT comparing ivermectin and other treatments with very late stage severe condition hospitalized patients, not showing significant differences between the treatments. Authors were unable to add a control arm due to ethical issues. The closest control comparison we could find is [\[Baqui\]](#), which shows 43% hospital mortality in the northern region of Brazil where the study was performed, from which we can estimate the mortality with ivermectin in this study as 47% lower, RR 0.53. Further, the study is restricted to more severe cases, hence the expected mortality, and therefore the benefit of treatment, may be higher. [\[Kishoria\]](#) restrict inclusion to patients that did not respond to standard treatment, provide no details on the time of the discharge status, and there are very large unadjusted differences in the groups, with over twice as many patients in the ivermectin group with age >40, and all patients over 60 in the ivermectin group.

Summarizing, the studies excluded are as follows, and the resulting forest plot is shown in Figure 21. The [supplementary data](#) shows results after restrictions and exclusions.

[Abbas], very minimal patient information, three different results for the recovery outcome, selective omission of the statistically significant recovery p-value, and other inconsistencies.

[Ahsan], unadjusted results with no group details.

[Beltran Gonzalez], major inconsistencies reported and the data is no longer available **[Chamie]**, although the authors state that it is available, and have shared it with an anti-treatment group.

[Borody], preliminary report with minimal details.

[Buonfrate], significant unadjusted group differences, with 3 times as many patients in the ivermectin arms having the baseline visit in a hospital setting, and arm C having large differences in baseline gender, weight, cough, pyrexia, and anosmia, excessive dose for arm C.

[Cadegiani], control group retrospectively obtained from untreated patients in the same population.

[Carvalho], concern about potential data issues.

[Carvalho (B)], concern about potential data issues.

[Carvalho (C)], minimal details of groups provided.

[de Jesús Ascencio-Montiel], unadjusted results with alternate outcome adjusted results showing significant changes with adjustments. Excluded results: death, mechanical ventilation, hospitalization, progression.

[Elavarasi], unadjusted results with no group details.

[Ferreira], unadjusted results with no group details, substantial unadjusted confounding by indication likely.

[Hazan], study uses a synthetic control arm.

[Hellwig], not a typical trial, analysis of African countries that used or did not use ivermectin prophylaxis for parasitic infections.

[IVERCOR PREP], minimal details provided.

[Kishoria], excessive unadjusted differences between groups.

[López-Medina], strong evidence of patients in the control group self-medicating, ivermectin widely used in the population at that time, and the study drug identity was concealed by using the name D11AX22.

[Mustafa], unadjusted results with no group details.

[Ravikirti], exclusion of patients in less severe condition, data/analysis concerns.

[Reis], multiple anomalies as per detailed analysis.

[Rezai], multiple critical issues, see study page.

[Rezai (B)], multiple critical issues, see study page.

[Roy], no serious outcomes reported and fast recovery in treatment and control groups, there is little room for a treatment to improve results.

[Samajdar], minimal details provided, unadjusted results with no group details, results may be significantly affected by survey bias.

[Soto], substantial unadjusted confounding by indication likely, substantial confounding by time possible due to significant changes in SOC and treatment propensity near the start of the pandemic.

[Soto-Becerra], substantial unadjusted confounding by indication likely, includes PCR+ patients that may be asymptomatic for COVID-19 but in hospital for other reasons.

[Szente Fonseca], result is likely affected by collinearity across treatments in the model.

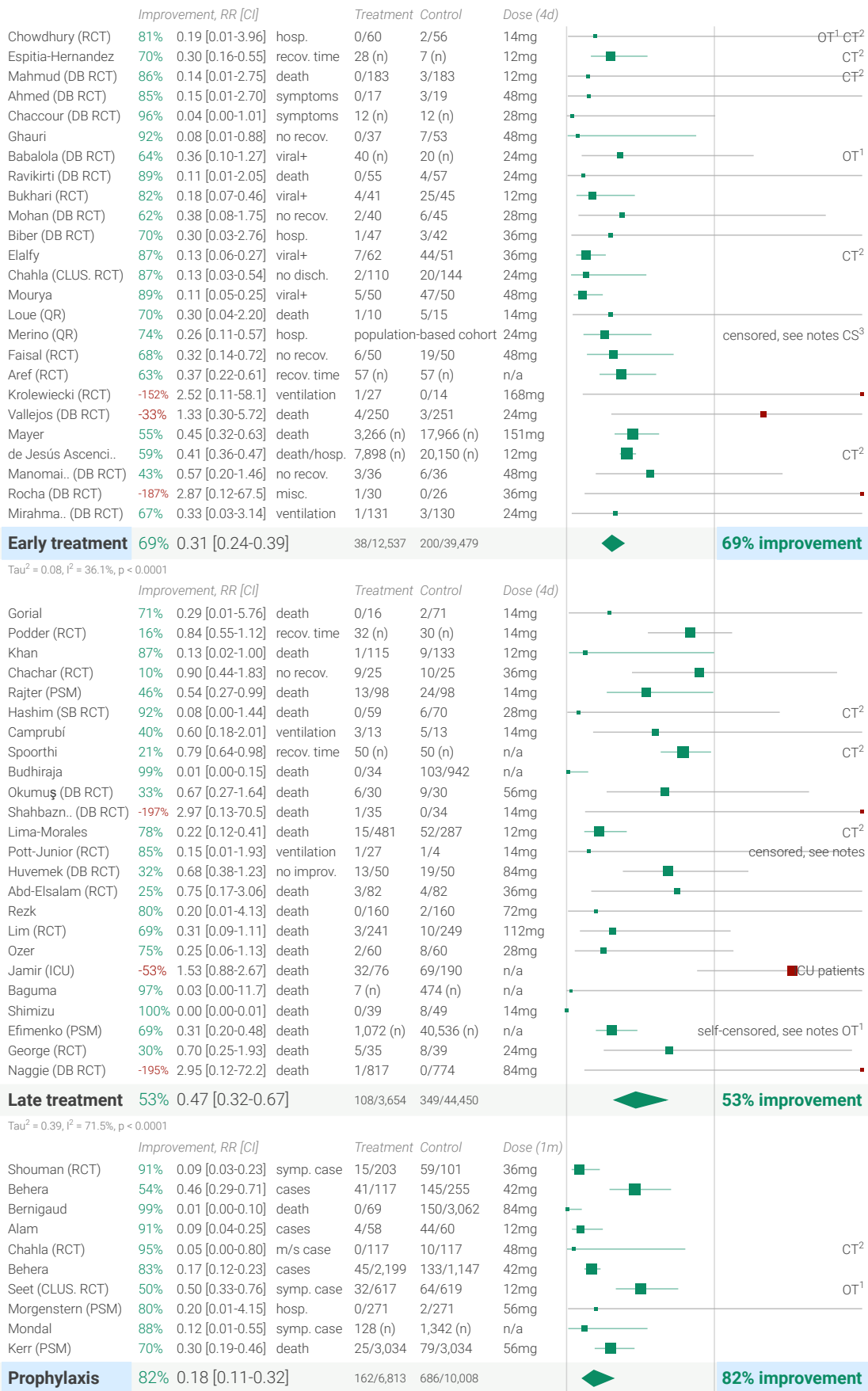
[Tanioka], not a typical trial, analysis of African countries that used or did not use ivermectin prophylaxis for parasitic infections.

[Thairu], significant confounding by time possible due to separation of groups in different time periods.

[Zubair], substantial unadjusted confounding by indication likely, unadjusted results with no group details.

59 ivermectin COVID-19 studies after exclusions

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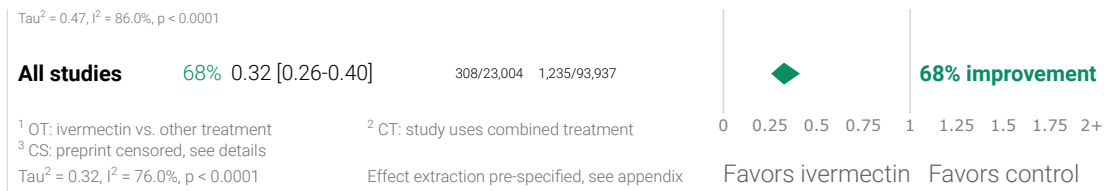


Figure 21. Random effects meta-analysis excluding studies with significant issues. Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details.

Heterogeneity

Heterogeneity in COVID-19 studies arises from many factors including:

Treatment delay. The time between infection or the onset of symptoms and treatment may critically affect how well a treatment works. For example an antiviral may be very effective when used early but may not be effective in late stage disease, and may even be harmful. Oseltamivir, for example, is generally only considered effective for influenza when used within 0-36 or 0-48 hours [*McLean, Treanor*]. Figure 22 shows a mixed-effects meta-regression for efficacy as a function of treatment delay in COVID-19 studies from 42 treatments, showing that efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.

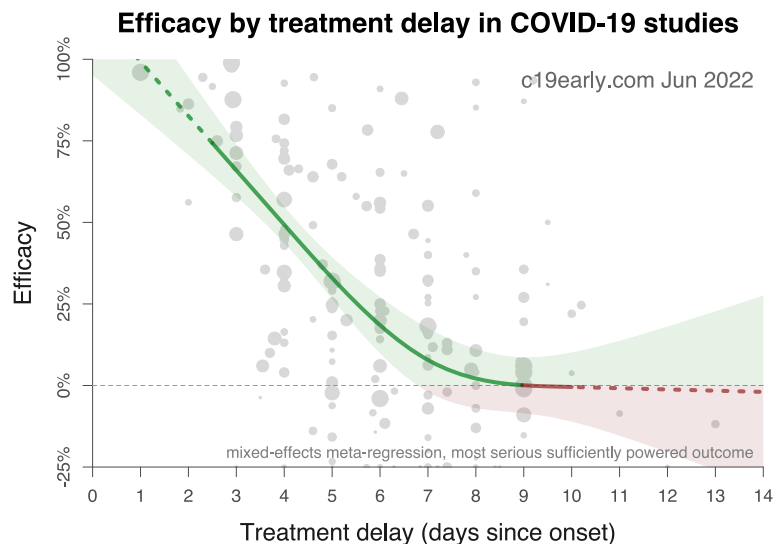


Figure 22. Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 42 treatments. Early treatment is critical.

Patient demographics. Details of the patient population including age and comorbidities may critically affect how well a treatment works. For example, many COVID-19 studies with relatively young low-comorbidity patients show all patients recovering quickly with or without treatment. In such cases, there is little room for an effective treatment to improve results (as in [*López-Medina*]).

Effect measured. Efficacy may differ significantly depending on the effect measured, for example a treatment may be very effective at reducing mortality, but less effective at minimizing cases or hospitalization. Or a treatment may have no effect on viral clearance while still being effective at reducing mortality.

Variants. There are many different variants of SARS-CoV-2 and efficacy may depend critically on the distribution of variants encountered by the patients in a study. For example, the Gamma variant shows significantly different characteristics [Faria, Karita, Nonaka, Zavascki]. Different mechanisms of action may be more or less effective depending on variants, for example the viral entry process for the omicron variant has moved towards TMPRSS2-independent fusion, suggesting that TMPRSS2 inhibitors may be less effective [Peacock, Willett].

Regimen. Effectiveness may depend strongly on the dosage and treatment regimen. Higher dosages have been found to be more successful for ivermectin [Babalola]. Method of administration may also be critical. [Guzzo] show that the plasma concentration of ivermectin is much higher when administered with food (Figure 23: geometric mean AUC 2.6 times higher). Many ivermectin studies specify fasting, or they do not specify administration. Fasting administration is expected to reduce effectiveness for COVID-19 due to lower plasma and tissue concentrations. Note that this is different to anthelmintic use in the gastrointestinal tract where fasting is recommended.

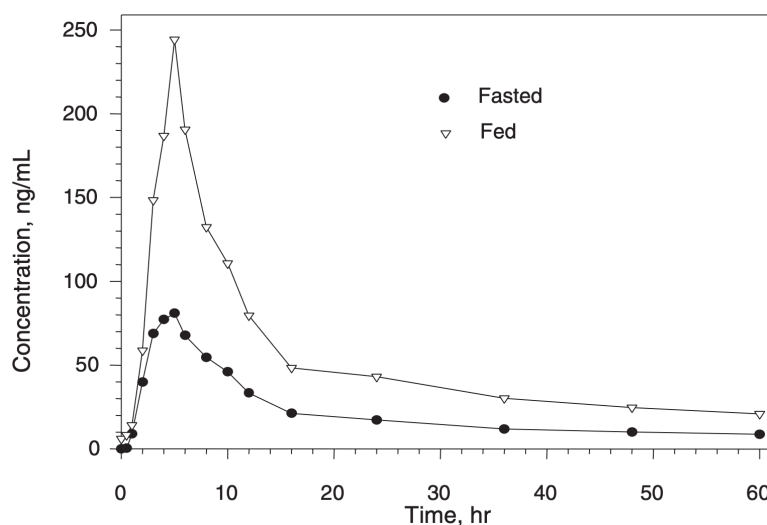


Figure 23. Mean plasma concentration (ng/ml) profiles of ivermectin following single oral doses of 30mg (fed and fasted administration), from [Guzzo].

Treatments. The use of other treatments may significantly affect outcomes, including anything from supplements, other medications, or other kinds of treatment such as prone positioning.

The distribution of studies will alter the outcome of a meta analysis. Consider a simplified example where everything is equal except for the treatment delay, and effectiveness decreases to zero or below with increasing delay. If there are many studies using very late treatment, the outcome may be negative, even though the treatment may be very effective when used earlier.

In general, by combining heterogeneous studies, as all meta analyses do, we run the risk of obscuring an effect by including studies where the treatment is less effective, not effective, or harmful.

When including studies where a treatment is less effective we expect the estimated effect size to be lower than that for the optimal case. We do not *a priori* expect that pooling all studies will create a positive result for an effective treatment. Looking at all studies is valuable for providing an overview of all research, important to avoid cherry-picking, and informative when a positive result is found despite combining less-optimal situations. However, the resulting estimate does not apply to specific cases such as early treatment in high-risk populations.

Ivermectin studies vary widely in all the factors above, which makes the consistently positive results even more remarkable. A failure to detect an association after combining heterogeneous studies does not mean the treatment is not effective (it may only work in certain cases), however the reverse is not true — an identified association is valid, although the magnitude of the effect may be larger for more optimal cases, and lower for less optimal cases. As above, the probability that an ineffective treatment generated results as positive as the 88 studies to date is estimated to be 1 in 39 billion. This result benefits from the fact that ivermectin shows some degree of efficacy for COVID-19 in a wide variety of cases. It also likely benefits from the fact that relatively few ivermectin trials to date have been designed in a way that favors poor results. However, more trials designed in this way are expected, for example the TOGETHER trial is testing ivermectin in locations known to have a high degree of self-medication and using low doses compared to current clinical recommendations as updated for current variants. As with a companion trial, this trial may also include very low-risk patients, include relatively late treatment while identifying as an early treatment trial, and use an active placebo (vitamin C). While we present results for all studies in this paper, the individual outcome and treatment time analyses are more relevant for specific use cases.

Discussion

Publication bias. Publishing is often biased towards positive results, which we would need to adjust for when analyzing the percentage of positive results. For ivermectin, there is currently not enough data to evaluate publication bias with high confidence. One method to evaluate bias is to compare prospective vs. retrospective studies. Prospective studies are likely to be published regardless of the result, while retrospective studies are more likely to exhibit bias. For example, researchers may perform preliminary analysis with minimal effort and the results may influence their decision to continue. Retrospective studies also provide more opportunities for the specifics of data extraction and adjustments to influence results. Figure 24 shows a scatter plot of results for prospective and retrospective studies. The median effect size for prospective studies is 67% improvement, compared to 70% for retrospective studies, showing no significant difference. **[Bryant]** also perform a funnel plot analysis, which they found did not suggest evidence of publication bias. Ivermectin has one of the most closely watched and closely examined evidence bases in history. Negative studies are submitted to us by multiple people immediately on publication. On the other hand, there is substantial evidence that journals are rejecting and delaying the publication of positive studies, for example by accepting a paper for review, holding it for some time, and then rejecting it without review **[Jerusalem Post, Kory (B)]**. One group performed prophylaxis and early treatment trials, with only the less positive study being formally published to date **[IVERCOR PREP, Vallejos]**, suggesting a negative publication bias. Dr. Eli Schwartz's **[Biber]** double blind RCT has been rejected without review by The Lancet and Clinical Infectious Diseases **[Fox]**. Authors of **[Efimenko]** do not plan to submit the very positive results to a journal, and have self-censored the conference publication, providing further evidence of a negative publication bias. Trials with pending and possibly delayed publication often involve researchers that may be restricted due to politics — publishing positive results may be incompatible with continued employment, whereas negative results can receive priority treatment at certain well-known journals, support the positions of employers or funding organizations, and receive substantial press.

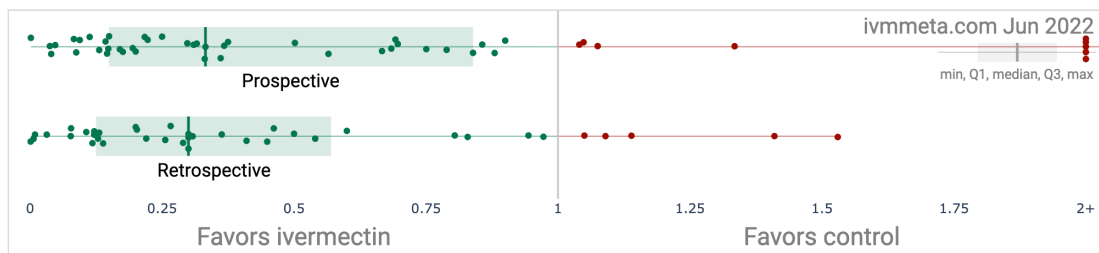


Figure 24. Prospective vs. retrospective studies.

News coverage of ivermectin studies is extremely biased. Only two studies to date have received significant press coverage in western media [*López-Medina, Reis*], both of which have multiple critical issues as discussed below.

Physician case series results. Table 4 shows the reported results of physicians that use early treatments for COVID-19, compared to the results for a non-treating physician (this physician reportedly prescribed early treatment for themselves, but not for patients [*medicospelavidacovid19.com.br*]). The treatments used vary between physicians. Almost all report using ivermectin and/or HCQ, and most use additional treatments in combination. A more detailed analysis requires information on the patient populations, however results are consistent with the extensive controlled trial evidence that shows a significant reduction in risk with early treatments, and improved results with the use of multiple treatments.

LATE TREATMENT						
Physician / Team	Location	Patients	Hospitalization		Mortality	
Dr. David Uip (*)	Brazil	2,200	38.6% (850)	Ref.	2.5% (54)	Ref.
EARLY TREATMENT - 32 physicians/teams						
Physician / Team	Location	Patients	Hospitalization	Improvement	Mortality	Improvement
Dr. Roberto Alfonso Accinelli 0/360 deaths for treatment within 3 days	Peru	1,265			0.6% (7)	77.5%
Dr. Mohammed Tarek Alam patients up to 84 years old	Bangladesh	100			0.0% (0)	100.0%
Dr. Oluwagbenga Alonge	Nigeria	310			0.0% (0)	100.0%
Dr. Raja Bhattacharya up to 88yo, 81% comorbidities	India	148			1.4% (2)	44.9%
Dr. Flavio Cadegiani	Brazil	3,450	0.1% (4)	99.7%	0.0% (0)	100.0%
Dr. Alessandro Capucci	Italy	350	4.6% (16)	88.2%		
Dr. Shankara Chetty	South Africa	8,000			0.0% (0)	100.0%
Dr. Deborah Chisholm	USA	100			0.0% (0)	100.0%
Dr. Ryan Cole	USA	400	0.0% (0)	100.0%	0.0% (0)	100.0%
Dr. Marco Cosentino vs. 3-3.8% mortality during period; earlier treatment better	Italy	392	6.4% (25)	83.5%	0.3% (1)	89.6%
Dr. Jeff Davis	USA	6,000			0.0% (0)	100.0%
Dr. Dhanajay	India	500			0.0% (0)	100.0%
Dr. Bryan Tyson & Dr. George Fareed	USA	4,375	0.2% (9)	99.5%	0.1% (3)	97.2%
Dr. Heather Gessling	USA	1,500			0.1% (1)	97.3%
Dr. Ellen Guimarães	Brazil	500	1.6% (8)	95.9%	0.4% (2)	83.7%
Dr. Syed Haider	USA	4,000	0.1% (5)	99.7%	0.0% (0)	100.0%
Dr. Mark Hancock	USA	24			0.0% (0)	100.0%
Dr. Mollie James	USA	3,500	1.1% (40)	97.0%	0.0% (1)	98.8%
Dr. Roberta Lacerda	Brazil	550	1.5% (8)	96.2%	0.4% (2)	85.2%
Dr. Ben Marble	USA	150,000			0.0% (4)	99.9%
Dr. Edimilson Migowski	Brazil	2,000	0.3% (7)	99.1%	0.1% (2)	95.9%
Dr. Abdulrahman Mohana	Saudi Arabia	2,733			0.0% (0)	100.0%
Dr. Carlos Nigro	Brazil	5,000	0.9% (45)	97.7%	0.5% (23)	81.3%
Dr. Benoit Ochs	Luxembourg	800			0.0% (0)	100.0%
Dr. Valerio Pascua one death for a patient presenting on the 5th day in need of supplemental oxygen	Honduras	415	6.3% (26)	83.8%	0.2% (1)	90.2%
Dr. Brian Proctor	USA	869	2.3% (20)	94.0%	0.2% (2)	90.6%

Dr. Anastacio Queiroz	Brazil	700			0.0% (0)	100.0%
Dr. Didier Raoult	France	8,315	2.6% (214)	93.3%	0.1% (5)	97.6%
Dr. Karin Ried up to 99yo, 73% comorbidities, av. age 63	Turkey	237			0.4% (1)	82.8%
Dr. Roman Rozencwaig patients up to 86 years old	Canada	80			0.0% (0)	100.0%
Dr. Vipul Shah	India	8,000			0.1% (5)	97.5%
Dr. Vladimir Zelenko	USA	2,200	0.5% (12)	98.6%	0.1% (2)	96.3%
Mean improvement with early treatment protocols		219,013	Hospitalization	95.1%	Mortality	93.7%

Table 4. Physician results with early treatment protocols compared to no early treatment. (*) Dr. Uip reportedly prescribed early treatment for himself, but not for patients [medicospelavidacovid19.com.br].

Funnel plot analysis. Funnel plots have traditionally been used for analyzing publication bias. This is invalid for COVID-19 acute treatment trials – the underlying assumptions are invalid, which we can demonstrate with a simple example. Consider a set of hypothetical perfect trials with no bias. Figure 25 plot A shows a funnel plot for a simulation of 80 perfect trials, with random group sizes, and each patient's outcome randomly sampled (10% control event probability, and a 30% effect size for treatment). Analysis shows no asymmetry ($p > 0.05$). In plot B, we add a single typical variation in COVID-19 treatment trials – treatment delay. Consider that efficacy varies from 90% for treatment within 24 hours, reducing to 10% when treatment is delayed 3 days. In plot B, each trial's treatment delay is randomly selected. Analysis now shows highly significant asymmetry, $p < 0.0001$, with six variants of Egger's test all showing $p < 0.05$ [Egger, Harbord, Macaskill, Moreno, Peters, Rothstein, Rücker, Stanley]. Note that these tests fail even though treatment delay is uniformly distributed. In reality treatment delay is more complex – each trial has a different distribution of delays across patients, and the distribution across trials may be biased (e.g., late treatment trials may be more common). Similarly, many other variations in trials may produce asymmetry, including dose, administration, duration of treatment, differences in SOC, comorbidities, age, variants, and bias in design, implementation, analysis, and reporting.

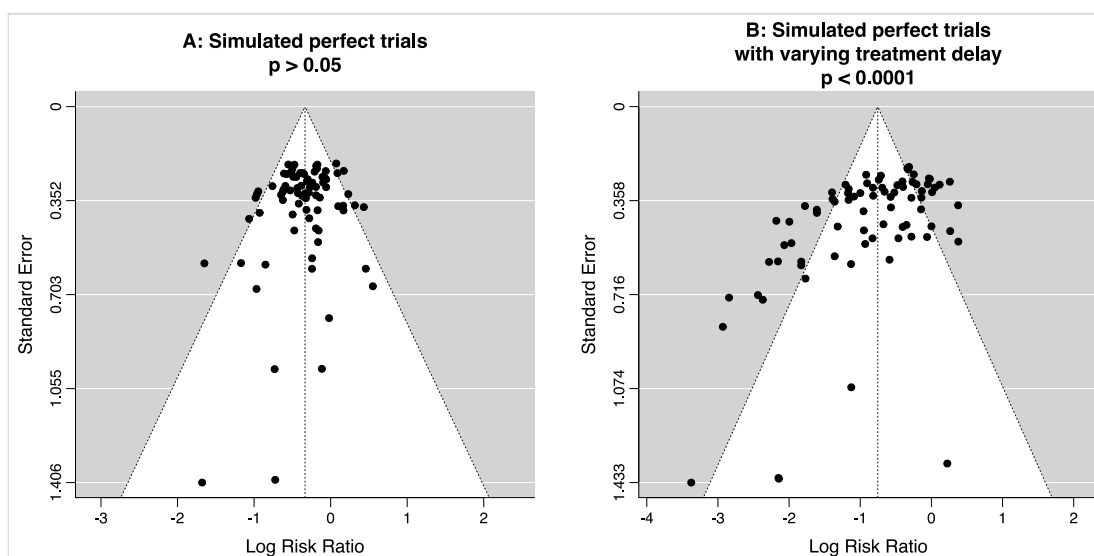


Figure 25. Example funnel plot analysis for simulated perfect trials.

In Vitro evidence on required concentration. Some people claim that [Caly] shows that therapeutic concentrations are not easily reached in humans. This is incorrect. The authors explain why their *in vitro* study cannot be used to determine the effective dose *in vivo*, and state that the concentration required is very unlikely to be an issue [Wagstaff]. The study used monkey kidney cells (the only choice at the time of the experiments), which lack adaptive immune responses and do not produce interferon. Authors also note that ivermectin accumulates in lung and other tissues, that subsequent experiments with lung cells show many times greater concentrations, and that the average lung concentration shown in modeling studies exceeds the effective level shown in their research. Authors note that ivermectin works with the immune system and a 1:1 ratio of drug to virus is unlikely to be required. In [Bray], author reply that "ivermectin's key direct target in mammalian cells is a not a viral component, but a host protein important in intracellular transport; the fact that it is a host-directed agent (HDA) is almost certainly the basis of its broad-spectrum activity against a number of different RNA viruses *in vitro*. The way a HDA can reduce viral load is by inhibiting a key cellular process that the virus hijacks to enhance infection by suppressing the host antiviral response. Reducing viral load by even a modest amount by using a HDA at low dose early in infection can be the key to enabling the body's immune system to begin to mount the full antiviral response before the infection takes control." In further research, authors note that they find efficacy for prophylactic use, and that smaller repeated doses are more effective than a single larger dose [Wagstaff].

Strongyloides. One theory for the beneficial effect of ivermectin for COVID-19 is related to strongyloides and the use of steroids — control group patients with strongyloides may be at risk due to steroid use, while ivermectin patients are protected. While this mechanism may contribute to efficacy in some cases, it is inconsistent with the data. If this was the case, we would expect to see greater benefit in late stage trials where steroids are used more often, and we would expect to see greater benefit for outcomes that occur after steroids are used. However, we see a very strong opposite effect for treatment time, and we see comparable or stronger efficacy for earlier outcomes.

The theory has gained renewed interest based on a new analysis [Bitterman]. However, this analysis is confounded by treatment delay, dose, conflicts of interest, and other factors, and the effect disappears when analyzing all studies, all RCTs, or all mortality results, as shown in Figure 26.

Although the first author has responded to the confounders on Twitter, we do not see mention of them in the paper. Author is also aware that the larger sets of all trials, all RCTs, or all mortality results do not show the effect, however we also do not see this mentioned in the paper. These omissions suggest investigator bias. Author claims they could not discuss these issues due to publication delays, however the paper was accepted Jan 31, 2022, and author was aware of the issues months before, for example discussing treatment delay and dose in Nov 2021. These confounders are also basic and not really possible to miss.

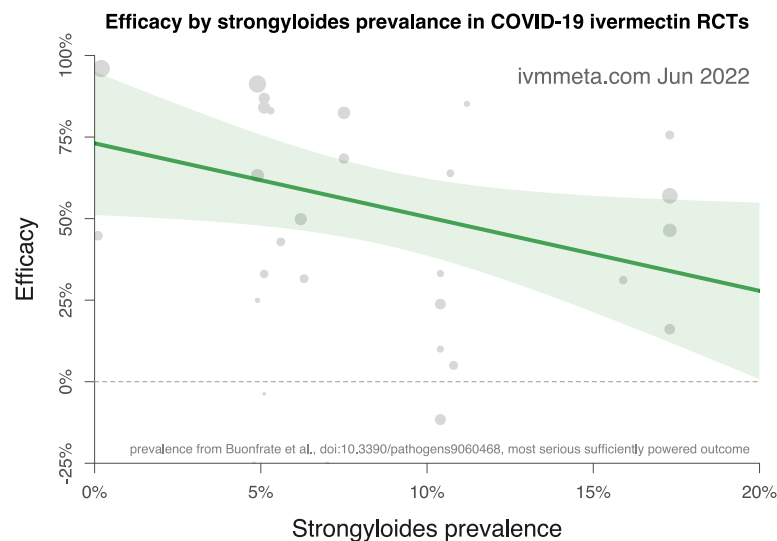
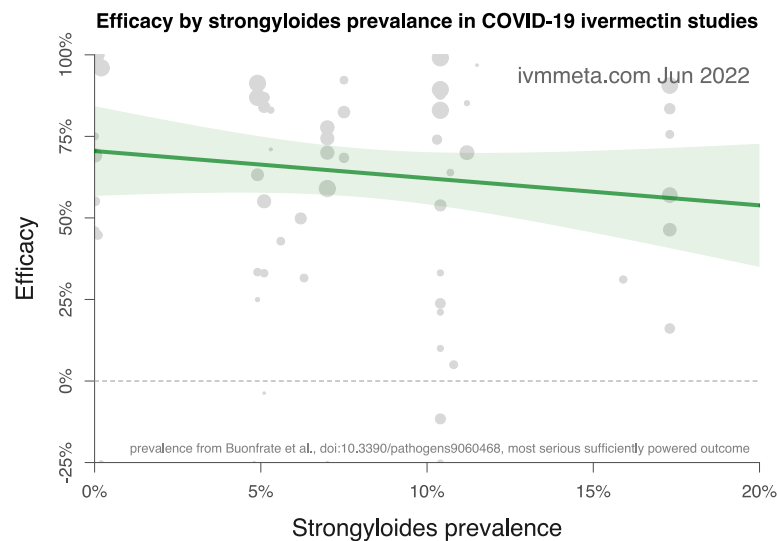
The meta analysis for [Hashim] includes critical patients, however these patients were always allocated to the treatment arm for ethical reasons, therefore including them is not logical and introduces substantial bias. According to the author response, this appears to have been known, suggesting investigator bias. Authors include [Shahbaznejad] where the only death was a critical patient that died within 24 hours of admission.

Although authors note following PRISMA guidelines, we do not see registration of the protocol or discussion thereof. We note that the current protocol is the result of multiple changes to the original methodology as posted on Twitter: from 3 groups to 2 groups, altering the included studies, and

switching from using one source for prevalence estimates to selecting estimate sources on a per study basis, which allows potential bias in the selection. Notably, this resulted in moving the Together Trial (Brazil) into the low prevalence category.

Author's results rely on trials with a very small number of mortality events – the high strongyloides prevalence group has trials with 1, 3, 4, and 13 events. Authors do mention limitations due to the small number of events and the reliability of strongyloides estimates.

Authors indicate no conflicts of interest, however the first author has been an investigator on a Pfizer trial, which may be NCT04092452, showing completion in January 2022 [clinicaltrials.gov, openpaymentsdata.cms.gov].



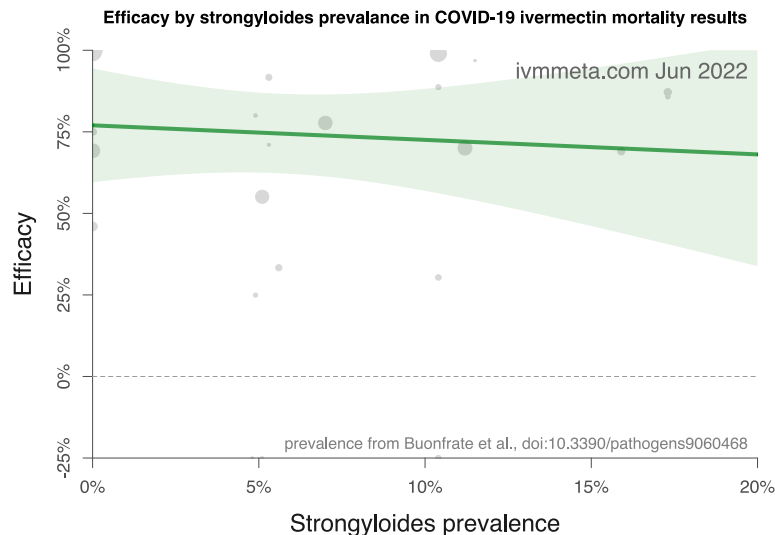


Figure 26. Mixed-effects meta-regression showing efficacy as a function of strongyloides prevalence for all studies, all RCTs, and all mortality results.

The following refers to the first author's analysis posted earlier on Twitter. The author selected 10 of the 88 studies, with 3 in a high strongyloides prevalence group where a greater benefit is seen. This was used to draw strong conclusions about the mechanism of ivermectin efficacy.

There are several limitations to this analysis. One of the 3 studies does not mention steroids in the list of SOC medications, while a second reports 6% usage for the control group. Author has added a fourth paper in a revised grouping with 11 studies.

We performed a similar analysis for all studies (except the 2 ecological studies), which shows no significant effect, with the high prevalence group actually showing lower improvement (51% [36-63%] vs. 68% [59-74%] for the low prevalence group). Details can be found in the [supplementary data](#). Results are similar when restricting to mortality results or when restricting to RCTs.

Why does the smaller analysis with 11 studies show a greater benefit in high strongyloides prevalence regions? The effect is based on relatively few events - 1, 3, 4, and 13 respectively for the high prevalence group. More importantly, the result is confounded by treatment delay and dose.

Treatment delay. All meta analyses combine heterogeneous studies which results in limitations. For example in pooled analysis we combine hospitalization and mortality. In terms of evaluating efficacy for COVID-19 treatments, reduction in hospitalization reasonably leads to reduction in mortality for high-risk populations. Both are indicators of efficacy, and both are valuable. In the largest series of COVID-19 treatment trials, hospitalization and mortality estimates are very similar. The same does not apply to treatment delay for antivirals. A trial showing efficacy with early treatment provides no information on late treatment, and a trial showing no efficacy with late treatment provides no information on early treatment. Ivermectin, as with many COVID-19 treatments, shows a strong treatment delay relationship — early treatment shows significantly higher efficacy.

The high prevalence group in the 11 study analysis has more early treatment trials, and the low prevalence group has more late treatment trials. The result is confounded by treatment delay, and reflects the greater efficacy of early treatment.

Only one trial in the high prevalence group is classified as late treatment, I-TECH, which was very close to the cutoff. Moreover, of all trials in the 11 trial analysis, this one uses the the highest dose.

Dose. The average dosage used in the high prevalence group is about twice the dose in the low prevalence group, and would be close to three times higher if the Together Trial was not moved to the low prevalence group. The result is confounded by dose, and reflects the greater efficacy of higher dosages.

Variants. Efficacy may vary based on variants. Notably, the Gamma variant was most common for one trial in the low prevalence group. This variant shows dramatically different characteristics [Zavascki], and clinicians report that significantly higher dosage and/or earlier treatment is required, as may be expected for variants where the peak viral load is significantly higher and/or reached earlier [Faria, Nonaka].

Conflicts of interest. Two trials have very high (>\$US1B) negative conflicts of interest which may introduce bias towards null effects. The trial in the low prevalence group shows a lower effect size. The trial in the high prevalence group also shows a lower effect size for the primary outcome. This trial shows a larger mortality effect, however with only one event this has very low significance.

Summary. In summary, the greater benefit in high strongyloides prevalence regions is only seen with the small subset of 11 trials and is not seen with all trials, or after restriction to mortality results, or restriction to RCTs. Within the 11 trial sample, all trials except one in the low prevalence group have confounding due to treatment delay and/or low dosage, where a lower effect size is expected. The only remaining trial in the group is unpublished, has an unknown treatment delay (a significant percentage of patients may have been treated very late), has very high negative conflicts of interest, and the Gamma variant was most common, in addition to other issues.

Conflicts of interest. Pharmaceutical drug trials often have conflicts of interest whereby sponsors or trial staff have a financial interest in the outcome being positive. Ivermectin for COVID-19 lacks this because it is off-patent, has many manufacturers, and is very low cost. In contrast, most COVID-19 ivermectin trials have been run by physicians on the front lines with the primary interest of finding the best methods to save human lives and minimize the collateral damage caused by COVID-19. While pharmaceutical companies are careful to run trials under optimal conditions (for example, restricting patients to those most likely to benefit, only including patients that can be treated soon after onset when necessary, ensuring accurate dosing), many ivermectin trials do not represent the optimal conditions for efficacy.

Two ivermectin trials to date involve very large financial conflicts of interest [López-Medina, Reis] — companies closely involved with the trial or organizers stand to lose billions of dollars if ivermectin efficacy becomes more widely known. The design of these trials favors producing a null outcome as detailed in [López-Medina, Reis]. Note that biasing an RCT to produce a false positive result is difficult (suppressing adverse events is relatively easy [Evans]), but biasing a trial to produce a false negative result is very easy — for example, in a trial of an antiviral that works within the first 24 hours of symptom onset, trial organizers only need to avoid treating people within the first 24 hours; or with a disease like COVID-19, organizers only need to select a low-risk population where most people recover quickly without treatment. We note that, even under the very suboptimal designs, these trials produced positive results, although without statistical significance.

Designed to fail. Additional upcoming trials including ACTIV-6, COVID-OUT, and PRINCIPLE have been designed in a way that favors finding no effect, with a number of methods including late treatment, selecting low-risk patients, fasting administration, very high conflict of interest medication sourcing, and dosing below current clinical practice. For discussion see [Goodkin].

COVID-OUT is enrolling relatively low risk patients (median age 46, 0.45 mean comorbidities), includes asymptomatic patients, and has a long delay between symptoms and treatment based on the sample collection delay in [\[Bramante\]](#).

PRINCIPLE paused enrollment in December 2021, claiming there was a supply issue [\[Henderson\]](#), however the manufacturer supplying the trial reported that they were not experiencing any supply issues. As of January 27, 2022, the trial was paused without explanation. As of February 11, 2022, the trial was open intermittently (twice daily between Sunday and Thursday), which would further decrease the chances of participants receiving relatively early treatment.

One patient reported their experience with one of the remote outpatient ivermectin/fluvoxamine trials: they were offered enrollment 7 days after symptoms (receipt of medication would be even later), were offered \$400 to participate, and reportedly target healthy people [\[twitter.com\]](#). ACTIV-6 also reportedly does not ship study medications on the weekend, adding additional delays [\[twitter.com \(B\)\]](#).

If these trials provide results for high-risk patients stratified by treatment delay, including patients treated within 1, 2, and 3 days of symptom onset (including any shipping delay), they may be informative even with limited dosing.

Early/late vs. mild/moderate/severe. Some analyses classify treatment based on early/late administration (as we do here), while others distinguish between mild/moderate/severe cases. We note that viral load does not indicate degree of symptoms – for example patients may have a high viral load while being asymptomatic. With regard to treatments that have antiviral properties, timing of treatment is critical – late administration may be less helpful regardless of severity.

Notes. The 88 studies are from 79 independent research teams. 4 studies compare against other treatments rather than placebo. Currently ivermectin shows better results than these other treatments, however ivermectin may show greater improvement when compared to placebo. 17 of 88 studies combine treatments, for example ivermectin + doxycycline. The results of ivermectin alone may differ. 4 of 39 RCTs use combined treatment, three with doxycycline, and one with iota-carrageenan. 1 of 88 studies currently has minimal published details available.

Meta analyses. Typical meta analyses involve subjective selection criteria, effect extraction rules, and study bias evaluation, which can be used to bias results towards a specific outcome. In order to avoid bias we include all studies and use a pre-specified method to extract results from all studies (we also present results after exclusions). The results to date are overwhelmingly positive, very consistent, and very insensitive to potential selection criteria, effect extraction rules, and/or bias evaluation. Additional meta analyses confirming the effectiveness of ivermectin can be found in [\[Bryant, Kory, Lawrie\]](#). Figure 27 shows a comparison of mortality results across meta analyses. [\[Kory\]](#) also review epidemiological data and provide suggested treatment regimens.

Ivermectin meta analysis mortality results ivmmeta.com Jun 2022

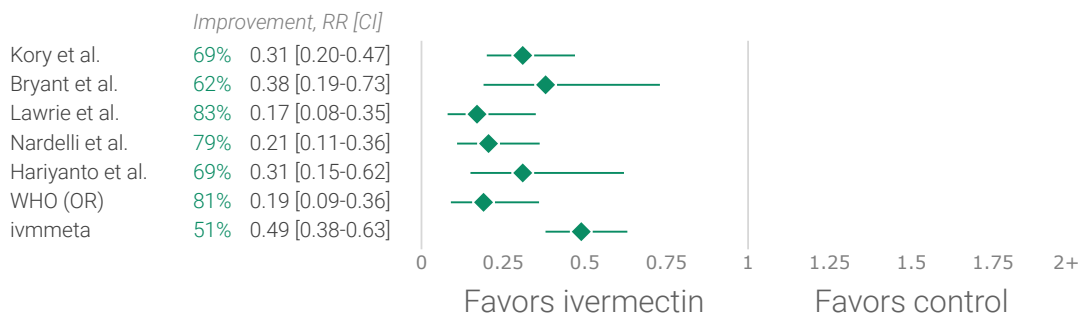


Figure 27. Comparison of mortality results from different meta analyses. OR converted to RR for [Kory, Nardelli]. OR displayed for [WHO]. WHO provides two results, one based on 5 studies and one based on 7, with no explanation for the difference. The result based on 7 studies is shown here, for which the details required to calculate the RR are not provided.

Evidence base. The evidence supporting ivermectin for COVID-19 far exceeds the typical amount of evidence used for the approval of treatments. [Lee] shows that only 14% of the guidelines of the Infectious Diseases Society of America were based on RCTs. Table 5 and Table 6 compare the amount of evidence for ivermectin compared to that used for other COVID-19 approvals, and that used by WHO for the approval of ivermectin for scabies and strongyloidiasis. Table 7 compares US CDC recommendations for ibuprofen and ivermectin.

Indication	Studies	Patients	Status
Strongyloidiasis [Kory (C)]	5	591	Approved
Scabies [Kory (C)]	10	852	Approved
COVID-19	88	132,948	Pending
COVID-19 RCTs	39	10,247	

Table 5. WHO ivermectin approval status.

Medication	Studies	Patients	Improvement	Status
Molnupiravir (UK)	1	775	50%	Approved
Budesonide (UK)	1	1,779	17%	Approved
Remdesivir (USA EUA)	1	1,063	31%	Approved
Casiri/imdevimab (USA EUA)	1	799	66%	Approved
Ivermectin evidence	88	132,948	63% [54-70%]	Pending

Table 6. Evidence base used for other COVID-19 approvals compared with the ivermectin evidence base.

	<i>Ibuprofen</i>	<i>Ivermectin (for scabies)</i>	<i>Ivermectin (for COVID-19)</i>
Lives saved	0	0	>500,000
Deaths per year	~450	<1	<1
CDC recommended	Yes	Yes	No
Based on	0 RCTs	10 RCTs 852 patients	39 RCTs 10,247 patients

Table 7. Comparison of CDC recommendations [Kory (C)].

WHO, Merck, FDA, NIH

WHO Analysis.

WHO updated their treatment recommendations on 3/30/2021 [WHO]. For ivermectin they reported a mortality odds ratio of 0.19 [0.09-0.36] based on 7 studies with 1,419 patients. They do not specify which trials they included. The report is inconsistent, with a forest plot that only shows 4 studies with mortality results. WHO's recommendation has not been updated for 455 days.

Despite this extremely positive result, they recommended only using ivermectin in clinical trials. The analysis contains many flaws [Kory (D)]:

- Of the 88 studies (39 RCTs), they only included 16.
- They excluded all 16 prophylaxis studies (3 RCTs).
- There was no protocol for data exclusion.
- Trials included in the original UNITAID search protocol were excluded.
- They excluded all epidemiological evidence, although WHO has considered such evidence in the past.
- They combine early treatment and late treatment studies and do not provide heterogeneity information. As above, early treatment is more successful, so pooling late treatment studies will obscure the effectiveness of early treatment. They chose not to do subgroup analysis by disease severity across trials, although treatment delay is clearly a critical factor in COVID-19 treatment, the analysis is easily done (as above), and it is well known that the studies for ivermectin and many other treatments clearly show greater effectiveness for early treatment.
- WHO downgraded the quality of trials compared to the UNITAID systematic review team and a separate international expert guideline group that has long worked with the WHO [Bryant].
- They disregarded their own guidelines that stipulate quality assessments should be upgraded when there is evidence of a large magnitude effect (which there is), and when there is evidence of a dose-response relationship (which there is). They claim there is no dose-response relationship, while the UNITAID systematic review team found a clear relationship, along with individual studies [Babalola].

- Their risk of bias assessments do not match the actual risk of bias in studies. For example they classify **[López-Medina]** as low risk of bias, however this study has many issues making the results unreliable **[Covid Analysis]**, even prompting an open letter from over 170 physicians concluding that the study is fatally flawed **[Open Letter]**. **[Beltran Gonzalez]** is also classified as low risk of bias, but is a study with very late stage severe condition high-comorbidity patients. There is a clear treatment delay-response relationship and very late stage treatment is not expected to be as effective as early treatment. Conversely, much higher quality studies were classified as high risk of bias.
- Although WHO's analysis is called a "living guideline", it is rarely updated and very out of date. As of May 14, 2021, four of the missing RCTs are known to WHO and labeled "RCTs pending data extraction" **[COVID-NMA]**. We added these 4, 4, 2, and one month earlier.
- A single person served as Methods Chair, member of the Guidance Support Collaboraton Committee, and member of the Living Systematic Review/NMA team.
- Public statements from people involved in the analysis suggest substantial bias. For example, a co-chair reportedly said that "the data available was sparse and likely based on chance" **[Reuters]**. As above, the data is comprehensive, and we estimate the probability that an ineffective treatment generated results as positive as observed to be 1 in 39 billion. The clinical team lead refers to their analysis of ivermectin as "fighting this overuse of unproven therapies ... without evidence of efficacy" **[Reuters]**, despite the extensive evidence of efficacy from the 88 studies by 922 scientists with 132,948 patients. People involved may be more favorable to late stage treatment of COVID-19, for example the co-chair recommended treating severe COVID-19 with remdesivir **[Rochwerg]**.

In summary, although WHO's analysis predicts that over 2 million fewer people would be dead if ivermectin was used from early in the pandemic, they recommend against use outside trials. This appears to be based primarily on excluding the majority of the evidence, and by assigning bias estimates that do not match the actual risk of bias in studies.

Use early in the pandemic was proposed by Kitasato University including the co-discoverer of ivermectin, Dr. Satoshi Ōmura. They requested Merck conduct clinical trials of ivermectin for COVID-19 in Japan, because Merck has priority to submit an application for an expansion of ivermectin's indications. Merck declined **[Yagisawa]**.

Merck Analysis.

Merck has recommended against ivermectin **[Merck]**, however this recommendation has not been updated for 509 days.

They stated that there is *"no scientific basis for a potential therapeutic effect against COVID-19 from pre-clinical studies"*. This is contradicted by many papers and studies, including **[Arévalo, Bello, Choudhury, de Melo, DiNicolantonio, DiNicolantonio (B), Errecalde, Eweas, Francés-Monerris (B), Heidary, Jans, Jeffreys, Kalfas, Kory, Lehrer, Li, Mody, Mountain Valley MD, Qureshi, Saha, Surnar, Udofia, Wehbe, Yesilbag, Zaidi, Zatloukal]**.

They state that there is *"no meaningful evidence for clinical activity or clinical efficacy in patients with COVID-19 disease"*. This is contradicted by numerous studies including **[Alam, Aref, Babalola, Baguma, Behera, Behera (B), Bernigaud, Budhiraja, Bukhari, Chaccour (B), Chahla, Chahla (B), Chowdhury, de Jesús]**

Ascencio-Montiel, Elalfy, Espitia-Hernandez, Faisal, Ghauri, Hashim, Huvemek, Kerr, Khan, Lima-Morales, Loue, Mahmud, Manomaipiboon, Mayer, Merino, Mohan, Mondal, Morgenstern, Mourya, Okumuş, Ravikirti (B), Seet, Shimizu].

They also claim that there is "a concerning lack of safety data in the majority of studies". Safety analysis is found in [Descotes, Errecalde, Guzzo, Kory, Madrid], and safety data can be found in most studies, including [Abd-El salam, Ahmed, Aref, Babalola, Behera (B), Bhattacharya, Biber, Bukhari, Camprubí, Carvallo (C), Chaccour (B), Chahla (B), Chowdhury, Elalfy, Espitia-Hernandez, George, Ghauri, Gorial, Hazan, Huvemek, Khan, Kishoria, Krolewiecki, Lima-Morales, Loue, López-Medina, Mahmud, Mohan, Morgenstern, Mourya, Okumuş, Pott-Junior, Seet, Shahbaznejad, Shouman, Spoorthi, Szenté Fonseca, Vallejos, Zubair].

Merck has a number of conflicts of interest:

- Merck has committed to give ivermectin away for free "as much as needed, for as long as needed" in the Mectizan® Donation Program [Merck (B)], to help eliminate river blindness.
- Merck has their own new COVID-19 treatments MK-7110 (formerly CD24Fc) [Adams] and Molnupiravir (MK-4482) [Jayk Bernal, Wikipedia]. Merck has a ~\$US1.2B agreement to supply molnupiravir to the US government, if it receives EUA or approval [Khan (B)]. Over \$US10B in near-term orders are expected if approved [Genetic Engineering and Biotechnology News].
- Ivermectin is off-patent, there are many manufacturers, and Merck is unlikely to be able to compete with low cost manufacturers.
- Promoting the use of low cost off-patent medications compared to new products may be undesirable to some shareholders.
- Japan requested Merck conduct clinical trials early in the pandemic and they declined. Merck may be reluctant to admit this mistake [Yagisawa].

For other concerns regarding Merck's statement and prior actions related to Vioxx, see [Scheim].

FDA Analysis.

The US FDA recommended against ivermectin on March 5, 2021, however they stated that "The FDA has not reviewed data to support use of ivermectin in COVID-19 patients to treat or to prevent COVID-19". There is still no indication that the FDA has reviewed the clinical trials 480 days later.

The FDA notes that they "received multiple reports of patients who have required medical support and been hospitalized after self-medicating with ivermectin intended for horses". The number of reports was 4 [Pfeiffer]. For comparison, acetaminophen overdose results in ~33,000 yearly hospitalizations in the USA (~12,000 unintentional) [Charilaou]. The FDA's recommendation may increase cases of self-medication with animal ivermectin, because it reduces the percentage of prescribing physicians.

They state that "Ivermectin is not an anti-viral", however many studies contradict this [Ahmed, Aref, Babalola, Biber, Bukhari, Buonfrate, Caly, Chowdhury, Elalfy, Espitia-Hernandez, Khan, Mahmud, Mohan, Mourya, Okumuş, Rezk, Thairu], including 10 RCTs.

They note that "some initial research is underway", however there had been many studies completed and published prior to the FDA recommendation [Ahmed, Alam, Babalola, Behera, Beltran Gonzalez, Bernigaud, Biber, Budhiraja, Bukhari, Cadegiani, Camprubi, Carvallo (C), Chaccour (B), Chachar, Chahla (B), Chowdhury, Elalfy, Espitia-Hernandez, Ghauri, Gorial, Hashim, Hellwig, Khan, Lima-Morales, López-Medina, Mahmud, Mohan, Okumuş, Podder, Rajter, Ravikirti (B), Shouman, Spoorthi], including 17 RCTs.

Sep 3, 2021: The FDA revised their statement slightly. They removed the false claim that ivermectin is not an antiviral, and they removed the statement that they have not reviewed the data. However, there is still nothing to indicate that they have reviewed the clinical trials. Indeed, they state "currently available data do not show ivermectin is effective against COVID-19" and "ivermectin has not been shown to be safe or effective for these indications", which are both false.

NIH Analysis.

Update: NIH has updated the recommendation, based heavily on the Together Trial, while making no mention of the impossible data, blinding, randomization, and protocol failures, or that the co-principal investigator privately reported that "There is a clear signal that IVM works in COVID patients".

NIH has reported that there is insufficient evidence to recommended for or against ivermectin [NIH]. A table with summaries of 7 studies is provided, dated Dec 16, 2021, and they reference another 23 studies without analysis, however there are 88 studies to date. No quantitative analysis is provided. The NIH recommendation is "insufficient evidence", indicating that they must review new evidence immediately. Lack of updates suggest bias.

The likely members of the panel have been revealed by FOIA requests [Yim (B)]. In the first request, all but two member names were redacted [drive.google.com], however all are visible in a second request [drive.google.com (B)]. Major conflicts of interest have been reported [trialsitenews.com, Yim (B)]. 7 of 9 panel members appear to have conflicts of interest. Submit Corrections or Updates

Prof. Adaora Adimora (adimora@med.unc.edu)	<ul style="list-style-type: none"> • Merck: advisory board, consultant, research support [covid19treatmentguidelines.nih.gov, trialsitenews.com (B)] • Gilead (maker of remdesivir): consultant, research support [files.covid19treatmentguidelines.nih.gov, tandfonline.com] "Adimora AA has received consulting fees from Viiv, and Gilead and her institution has received funding from Gilead for her research" • Open Payments shows \$62,000 from Merck and \$88,000 from Gilead [openpaymentsdata.cms.gov (B)]
Prof. Roger Bedimo (roger.bedimo@va.gov)	<ul style="list-style-type: none"> • Merck: advisory board [covid19treatmentguidelines.nih.gov, trialsitenews.com (B)] • Gilead: honoraria [files.covid19treatmentguidelines.nih.gov] • Open Payments shows \$149,000 from Merck, \$76,000 from Sanofi, and \$23,000 from Gilead [openpaymentsdata.cms.gov (C)]
Prof. Rajesh Gandhi (rgandhi@mgh.harvard.edu)	<ul style="list-style-type: none"> • Gilead: grants, advisory board, personal fees [nejm.org, rmed.acponline.org] "Dr. Gandhi reports grants and personal fees

	<p>from Gilead, personal fees from Merck, grants and personal fees from Theratechnologies, grants from ViiV, grants from Janssen."</p> <ul style="list-style-type: none"> • Merck: advisory board and personal fees [files.covid19treatmentguidelines.nih.gov, nejm.org, rmed.acponline.org] • Janssen: grants [nejm.org] • Open Payments shows \$45,000 from Merck and \$10,000 from Gilead [openpaymentsdata.cms.gov (D)]
Prof. David Glidden (david.glidden@ucsf.edu)	<ul style="list-style-type: none"> • Merck: advisory board [covid19treatmentguidelines.nih.gov, trialsitenews.com (B)] • Gilead: consultant [covid19treatmentguidelines.nih.gov, files.covid19treatmentguidelines.nih.gov]
Prof. Roy Gulick (rgulick@med.cornell.edu)	<ul style="list-style-type: none"> • Merck: grants [web.archive.org] (deleted from current version [medscape.org]) "Roy M. Gulick, MD, MPH, has disclosed that he has received grants for clinical research from Abbott, Boehringer Ingelheim, Merck, Pfizer, Schering, and Tibotec, and has received grants for educational activities from Gilead and Monogram. Dr. Gulick has also disclosed that he has served as an ad-hoc advisor or consultant to Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Pfizer, Schering, and Tibotec", principal investigator on A5391 with funding in part from Merck [actgnetwork.org] • Pfizer: grants and ad-hoc advisor or consultant [web.archive.org] (deleted from current version [medscape.org]) • Gilead: grants and ad-hoc advisor or consultant [web.archive.org] (deleted from current version [medscape.org]) • GlaxoSmithKline: ad-hoc advisor or consultant [web.archive.org] (deleted from current version [medscape.org]) • NIAID/NIH: grants [acpjournals.org, vivo.weill.cornell.edu]
Prof. Susanna Naggie (susanna.naggie@duke.edu)	<ul style="list-style-type: none"> • Gilead: grants, travel/meeting support [covid19treatmentguidelines.nih.gov, files.covid19treatmentguidelines.nih.gov, rmed.acponline.org] • AbbVie, NIH: grants [rmed.acponline.org] • Vir Biotechnology: advisory board, stockholder [covid19treatmentguidelines.nih.gov] • Ivermectin trial grant: \$155 million grant after the insufficient evidence recommendation [trialsitenews.com (B)]

	<ul style="list-style-type: none"> • Open Payments shows \$2.4 million from AbbVie, \$1.2 million from Gilead, \$34,000 from Janssen, and \$19,000 from Merck [openpaymentsdata.cms.gov (E)]
Prof. Andrew Pavia (andy.pavia@hsc.utah.edu)	<ul style="list-style-type: none"> • Merck: consultant [files.covid19treatmentguidelines.nih.gov, rmed.acponline.org] • Genentech: consultant [files.covid19treatmentguidelines.nih.gov] • GlaxoSmithKline: consultant [rmed.acponline.org] • Open Payments shows \$14,000 from Pfizer, \$5,000 from Merck, and \$4,000 from Janssen [openpaymentsdata.cms.gov (F)]

Conclusion

Ivermectin is an effective treatment for COVID-19. Treatment is more effective when used early. Meta analysis using the most serious outcome shows 63% [52-71%] and 83% [74-89%] improvement for early treatment and prophylaxis, with similar results after exclusion based sensitivity analysis, for primary outcomes, for peer-reviewed studies, and for RCTs. Statistically significant improvements are seen for mortality, ventilation, ICU admission, hospitalization, recovery, cases, and viral clearance. All remain significant after exclusions. 56 studies from 51 independent teams in 22 different countries show statistically significant improvements in isolation (39 for primary outcomes, and 36 for the most serious outcome). Results are very robust — in worst case exclusion sensitivity analysis 55 of 88 studies must be excluded to avoid finding statistically significant efficacy.

Responses

Inconclusive meta analyses.

[[Popp, Roman](#)] provide meta analyses that show positive effects without reaching statistical significance. The primary methods used that result in a lack of statistical significance are the exclusion of the majority of the evidence base, and division of the remaining subset. For more details see the [study notes](#).

Primary outcome analysis.

We use fixed pre-specified effect extraction to avoid bias and to focus on the most clinically relevant results. For comparison, we have also performed analysis using the primary outcome of studies (shown in the [supplementary data](#)), with results showing similar effect sizes. Prophylaxis results are very similar with 100% (16 of 16) positive effects. Early treatment shows 91% (32 of 35) positive effects, improved due to the very small event count negative serious outcomes in Krolewiecki, Vallejos, and Buonfrate no longer having priority. Late treatment shows 73% (27 of 37) positive effects, reduced slightly, primarily due to viral clearance results being the primary outcome in some studies, and viral clearance being less successful with late treatment. Overall, the primary outcome analysis shows 85% (75 of 88) positive effects, compared to 84% (74 of 88) in the main protocol analysis.

Meta analysis should not combine heterogeneous studies.

All meta analyses combine heterogeneous studies, because all studies differ in one or more ways, including patient demographics, treatment delay distribution, effect measured, SARS-CoV-2 variants, and treatment regimens (note that this is different to heterogeneity caused by bias). Combining heterogeneous studies may obscure efficacy - for example if treatment within 24 hours is twice as effective as treatment within 48 hours and we include studies with later treatment; or if a treatment is effective at reducing mortality but has no effect on viral clearance and we include viral clearance studies. Including studies that are further from the optimal treatment situation will reduce the observed effect size. This can be seen in the treatment delay analysis - late treatment is less effective and including late treatment studies lowers the effect size. For any negative meta analysis, we must consider if the treatment is effective but only in a subset of the situations covered by the studies (or a situation not covered by any study, for example few treatments have studies with a treatment delay ≤ 24 hours).

BBC response.

Update: authors indicated that their data would be available "soon" as of Sep 14, 2021, however it has not been released over 286 days later, therefore it is not possible to analyze their methods regarding ivermectin research in detail. However, Dr. Sheldrick posted false and defamatory accusations regarding a highly respected physician that has saved countless lives before and during the pandemic. In this case, detailed methods were published, revealing highly flawed analysis, and a basic misunderstanding of statistics, as detailed by multiple statisticians [Fenton, twitter.com (C)]. Author has now deleted the blog post and taken their Twitter account private. Further, we note that the team's disregard for major issues with the Together Trial, López-Medina et al., and Beltran Gonzalez et al. suggest substantial bias.

A BBC article raises questions due to data issues in some studies, based on an analysis from a team of researchers. One of the researchers reports that data in some trials could have been manipulated, while noting that human error can not be ruled out. Others in the team directly accuse authors of malfeasance. Regardless of the cause, concern over these studies is valid. Currently, 2 studies have been retracted, one was withdrawn by a preprint server, and another has been reported as pending retraction, although the journal reports that no retraction is pending. None of these studies are in our analysis.

Existence of some lower quality studies is typical in large evidence bases. The percentage of studies with issues is not greater than reported averages, and is not close to removing evidence of efficacy (and may actually improve evidence as detailed below). We performed an absolute worst case sensitivity analysis, where positive studies are excluded in order of the effect size, with the largest effect first. **62%, or 55 of 88 studies must be excluded to avoid finding statistically significant efficacy (this is in addition to the four papers not in this analysis).**

The summary statistics from meta analysis necessarily obscure most of the information in the evidence base. For those that have read all of the research, knowledge of efficacy is supported by extensive additional information, including for example relationships between outcomes within a study, dose-response relationships within and across studies, treatment delay-efficacy relationships within and across studies, variant-efficacy relationships, etc. Notably, removal of Elgazzar, Samaha, and Niaee improve the treatment delay-efficacy and dose-response relationships and may further increase confidence when considering all information.

Concerns about [Cadebiani, Carvallo, Carvallo (B), Carvallo (C)] have also been reported. All of these studies are excluded in our exclusion analysis.

	Studies	Prophylaxis	Early treatment	Late treatment	Patients
With GMK/BBC exclusions	59	82% [68-89%]	69% [61-76%]	53% [33-68%]	116,941

RCTs w/GMK/BBC exc.	31	84% [25-96%]	66% [54-75%]	29% [4-47%]	6,967
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Percentage improvement with ivermectin treatment after exclusion of all studies reported by this team

We note that, while malfeasance cannot be ruled out, reported concerns may also be caused by typos, data collection errors not affecting analyzed outcomes, and expected results from multiple tests. Authors, without any prior registration or statistical analysis plan, perform thousands of statistical tests across data in the studies and report results without correcting for multiple tests. For example, reporting the occurrence of a 1 in 1,000 event as evidence of randomization failure, while performing more than this number of tests across studies.

This group often dismisses studies based on an arbitrary statistical significance threshold for a specific outcome, a misunderstanding of statistics *[Amrhein]*, and indefensible as a pre-filter in meta analysis.

This group has made many claims unsupported by the data. For Niaee, one author claimed the study "made a HUGE difference". It has no effect on early treatment or prophylaxis. For late treatment, which is not recommended, the change was relatively minor. For Elgazzar, the author claimed that it could be "the most consequential medical fraud ever committed". There was almost no difference in our analysis after removing this paper (excluding 1 of 91 studies has very little effect, and the exclusion actually improves the treatment delay-response relationship).

Statements by the group suggest significant bias. The main author first referred to ivermectin as "something else to debunk" in December 2020, and later as a "horse dewormer". Another group member has called for charging scientists that recommend vitamin D with "crimes against humanity".

The group has made claims about all ivermectin evidence based on the existence of some studies with issues. It is inappropriate to generalize about the entire group of 922 scientists and researchers based on the mistakes or actions of a few individuals.

This group has focused on finding issues in papers reporting large positive effects, which introduces a significant bias. Notably, the few studies that contribute most to minimizing the effects in meta analysis include studies with very high conflicts of interest and many reported protocol violations and data issues, however this group disregards all of these issues.

The article claims "The largest and highest quality ivermectin study published so far is the Together trial" which "found no benefit", however this study has not been published, is one of the lowest quality trials with many documented design, execution, and analysis issues, has extremely high conflicts of interest, there is a history of inaccurate reporting prior to publication for a previous treatment in the same trial, and the trial actually reported 18% lower mortality (not statistically significant).

The article reports that 26 studies were examined, however there are 91 studies, authors have not reported their results for all 26, and authors have not provided their data after repeated requests. Currently they have not even provided a list of the 26 studies.

The group has an excessive focus on RCTs, which have a fundamental bias against finding an effect for interventions like ivermectin that are widely known and easily available — patients that believe they need treatment are more likely to decline participation and take the treatment *[Yeh]* (this does not apply to the typical pharmaceutical trial of a new drug that is otherwise unavailable and unfamiliar).

The main author of the group is also against vitamin D. Of the 82 vitamin D COVID-19 treatment studies, author suggests only one trial is worth looking at [*Murai*]. This gives us a simple case to examine potential bias. [*Murai*] is a small trial providing no statistically significant effects (mortality $p = 0.43$, other outcomes are positive while also not significant). Author acknowledges that the trial is too small for a conclusion. More importantly, this trial provides no information about whether vitamin D reduces the risk of a serious COVID-19 case, because the patients in this trial already had a serious COVID-19 case (90% already on oxygen treatment at baseline). Author does not mention this. The trial also has poorly matched arms in terms of gender, ethnicity, hypertension, diabetes, and baseline ventilation, all favoring the control group. Further, this study uses an inappropriate form of vitamin D — cholecalciferol. In reality physicians would use calcifediol or calcitriol with late stage treatment, because they avoid a very long delay for conversion. We are unaware of a reason to use cholecalciferol in this case (other than to produce a null result). In summary, author's chosen study is the study providing the least useful information from the 82 vitamin D treatment studies to date, suggesting biased analysis.

We fully support this team's effort to clean up the evidence base. This is extremely valuable and improves the integrity of the evidence base (and the accuracy if done equally for all studies). We hope this or other teams can do the same for all treatments. However the analysis plan should be published, details of all tests should be provided, results should be corrected for multiple testing, results for all studies and tests should be provided, and equal attention should be given to studies with non-statistically significant results, especially those with major reported data issues that have been disregarded by this team (for example data suggesting substantial protocol violations including confounding by time in [*Reis*] and control arm use of treatments in [*López-Medina*]).

For coverage of other errors in the BBC article, and illumination of the stark contrast between Dr. Lawrie's response to the BBC before publication and what they chose to report, see [*BiRD Group, Campbell, Elijah, Lawrie (B)*].

More details can be found in the following response regarding the main author of this group.

GMK response.

Update: GMK indicated that their data would be released "soon" as of Sep 14, 2021, however it has not been released over 286 days later. Further, we note that GMK's disregard for major issues with the Together Trial, ACTIV-6, López-Medina et al., and Beltran Gonzalez et al. suggest substantial bias.

Incorrect, misleading, hyperbolic, and unsupported statements have been made by an influential anti-treatment Twitter personality, journalist, and PhD student known for defending Monsanto Roundup against carcinogenic claims (later settled for \$US 11 billion). Author is notable as the only known researcher that reports having read a majority of the 91 (including retracted) studies, but does not find the evidence to be positive. However, their opinion appears to have been formed before reading the studies — they first referred to ivermectin as "*something else to debunk*". We note that the author has made valuable contributions identifying significant issues with some studies, which has helped to improve the quality of the ivermectin evidence base, and has improved the dose-response and treatment delay-response relationships.

Analysis with GMK's recommended exclusions can be found in the supplementary data, which shows 44% [29-56%] improvement, $p = 0.0000026$.

Author has been paid for writing anti-treatment articles, and has also referred to ivermectin as a "*horse dewormer*". Author has experienced personal tragedy with multiple family members having died of COVID-19, which may introduce a bias against acknowledging errors in treatment advice.

Author's attempt to discredit ivermectin research centers on the fundamentally false assertion that excluding a small number of lower quality trials results in a negative outcome. It should be clear from the forest plot that this is not possible, but we can be more specific. We perform a worst case sensitivity analysis, where positive studies are excluded in order of the effect size, with the largest effect first. How many studies do we need to exclude before the meta analysis RR has a confidence interval exceeding 1.0? **62%, or 55 of 88 studies must be excluded to avoid finding statistically significant efficacy.** As with all data in this paper, this analysis will automatically update as the evidence base evolves. Also note that this is after exclusion of withdrawn papers - one has never been in this analysis, the second was removed on the same day it was withdrawn, and the other two were removed in advance of retraction based on author's notification that retraction is pending (only one has been retracted, the journal for Niaee et al. has reported that no retraction is pending).

Author claims that we include several papers that are already excluded in the 10 exclusion analyses.

Author claims that there is a greater percentage of low quality studies for ivermectin and COVID-19 compared to other treatments. This is unsupported for such a large evidence base, and does not match previous studies.

Author often makes a basic error by equating positive effects that are not statistically significant at a specific level with "no effect", a misunderstanding of statistics [Amrhein]. For example, if a study reports 50% improvement with a p value of 0.1, we cannot say that the study shows the treatment is ineffective, or in the words of the author shows "no benefit at all". Author repeatedly makes false claims in this way.

On Sep 14, 2021, author indicated that their team had reviewed about 30 ivermectin studies and their data would be available soon, however it has not been released nine months later.

Author appears to favor pharmaceutical company affiliated/operated trials. For example, the author has no problem with the lack of IPD for many pharmaceutical affiliated COVID-19 trials that support the author's treatment positions, yet considers the lack of IPD in a positive ivermectin trial to be problematic. Author believes the pharmaceutical affiliated Together Trial is the highest quality trial so far, yet not only have the authors declined to release IPD that they previously pledged to release, there was not even a preprint when GMK made the statement, and the trial has many critical and serious flaws, extremely high conflicts of interest, and a history of inaccurate reporting prior to publication for another treatment arm. GMK has subsequently published a paper with one of the original co-lead's of the Together Trial (who later joined the trial DSMC).

Author disregards treatment delay in analysis, which results in incorrect conclusions. For example, author claims that the RECOVERY trial proved that another treatment is not effective, and would provide definitive data if the same was done for ivermectin. The trial provided valuable data on very late use (9 days after symptoms) with an excessively high dose and very late stage patients. However, it did not provide information on early treatment. Oseltamivir, for example, is generally only considered effective for influenza when used within 0-36 or 0-48 hours [McLean, Treanor]. Paxlovid was tested with a maximum of 3 days from symptom onset (the mean delay is unknown). For ivermectin, author believes the PRINCIPLE trial will provide strong data on efficacy, however this trial includes low risk patients less than 15 days from symptom onset, and may only provide information on late treatment in a low risk population. Figure 28 shows a mixed-effects meta-regression for efficacy as a function of treatment delay in COVID-19 studies from 42 treatments. Efficacy declines rapidly with treatment delay.

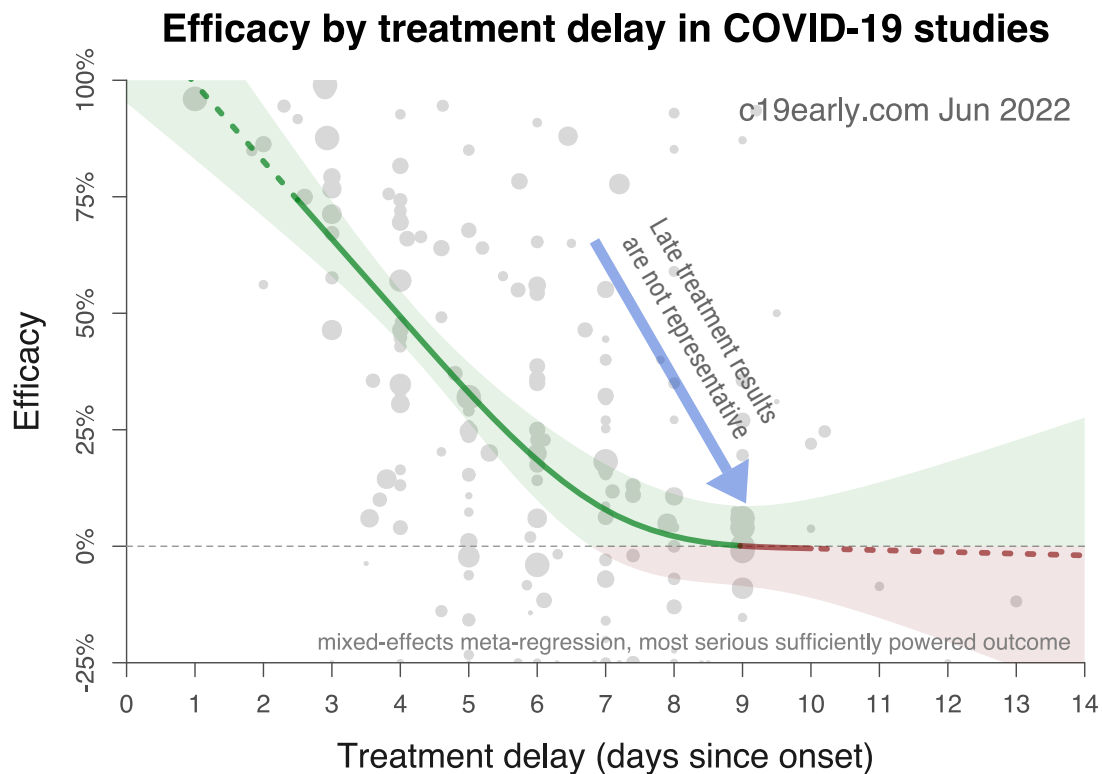


Figure 28. GMK believes that results for treatment delayed 9 days from symptom onset provides definitive information on treatment efficacy, however early treatment is known to be critical for antivirals, as confirmed by meta-regression of studies from 42 treatments.

Author has an unwarranted focus on a specific outcome (mortality) and a specific subset of trials (RCTs). This would be reasonable in many cases when sufficient high-quality data is available, however this is not the case for off-patent COVID-19 treatment trials, where RCTs often involve delayed treatment, low-risk patients where mortality is rare, or very high conflicts of interest. Widely accepted and effective (for specific variants) treatments like casirivimab/imdevimab, bamlanivimab, and sotrovimab were all approved without statistically significant mortality benefits. Other outcomes are also important – accelerating viral clearance, and reducing cases, hospitalization, ICU admission, ventilation, etc. are all very valuable, for example reducing serious "long COVID" problems, reducing transmission of the virus, and reducing the burden on the healthcare system. These outcomes are also likely to correlate with reduced mortality among larger or higher-risk populations. We note that there is extensive evidence for the mortality outcome when not restricting to RCTs. RCTs have mostly been run with relatively low risk populations where mortality is low, leading to limited statistical significance. However RCTs are inherently biased towards low mortality and towards not finding an effect in this case – ivermectin is well-known to be beneficial for COVID-19 and is easily available, therefore participants that believe they may be at serious risk are more likely to decline participation in the RCT and take the recommended medications. Patients that do choose to participate are also more likely to have low adherence. This bias of RCTs is likely to be even larger in locations where ivermectin is widely used in the community and very easily obtained, which correlates with the observed RCT results.

Author suggests that we have chosen the wrong outcome in some cases. While mistakes are possible, for example we corrected errors with Espitia-Hernandez et al. and Jain et al., the claims made suggest that the author has not read the studies and/or our protocol carefully. Details are below. We note that the author disregards the existence of the individual outcome analyses and the primary outcome analysis.

Most errors have not been corrected over ten months later. Many false, misleading, and defamatory statements continue to be available, highly-ranked in search results, and highly influential. Other errors include:

- that excluding Elgazzar et al. completely changes the results and could be "*the most consequential medical fraud ever committed*". Excluding 1 of 91 studies has very little effect, and the exclusion improves the treatment delay-response relationship.
- that Niaee et al. "*made a HUGE difference*". It has no effect on early treatment or prophylaxis. For late treatment, which is not recommended, the change was relatively minor, and the exclusion improves the treatment delay-response relationship.
- making basic errors suggesting very superficial reading of studies, for example claiming the RR in Szente Fonseca is the risk of being treated.
- making basic errors suggesting very superficial reading of this paper, for example claiming that a result for prophylaxis studies is based on the number of patients from all studies.
- equating a high degree of COVID-19 in a country partially adopting a treatment with a lack of efficacy, disregarding obvious confounding such as heavily affected areas being more likely to adopt treatment (analysis of results in regions or time periods adopting treatment, while not equivalent to controlled studies, is more informative and shows efficacy [*Chamie-Quintero, Chamie-Quintero (B), Merino, Ontai*]).
- confusing heterogeneity due to dose, treatment delay, etc. and due to bias.
- disregarding treatment delay to dilute or obscure effects by including late treatment (author has also used this method with other treatments).
- disregarding the existence of specific outcome analyses, RCT analysis, and exclusion-based sensitivity analysis.
- suggesting that efficacy over longer periods is not possible because ivermectin has a half-life of "*about a day*". Author disregards known efficacy for other conditions over much longer periods, and mischaracterizes the half-life. Antiparasitic efficacy can persist for several months after a single dose [*Canga*]. Plasma half-life is longer in some studies, and significant plasma concentration can persist for over 2 weeks in some patients [*Muñoz*]. More importantly, ivermectin is highly lipophilic and may accumulate in the lung and other tissues where concentrations may be many times higher [*Chaccour (C), Chiu*].
- misunderstanding funnel plot analysis and explanations other than selective reporting (and providing no evidence of unreported negative studies, while there is substantial evidence of difficulty publishing positive studies [*Jerusalem Post, Kory (B)*]).
- suggesting that it is impossible to combine evidence from mortality and hospitalization (for example), but combining late treatment and early treatment in order to obscure efficacy (if a treatment reduces disease severity requiring hospitalization, reduced mortality in at-risk populations logically follows, whereas lack of efficacy several days after onset can not be extrapolated to early treatment — treatments for a viral infection are often less effective when delayed).
- making serious claims about individual studies without contacting authors (for example claiming patients were excluded for reaching the endpoint too quickly in one study, whereas authors report exclusions due to baseline negative status).

- author is unaware of different variants, suggesting that results should be identical for treatment at a given delay, even when the predominant variants have markedly different peak viral load, time to peak viral load [*Faria, Karita, Nonaka*], and mortality (for example Gamma vs. non-Gamma aHR 4.73 [1.15-19.41] [*Zavascki*]).

The cases where author suggests we have chosen the wrong outcome indicate that the author has not read the studies and/or our protocol carefully:

- suggesting that the risk of a good outcome should be selectively used instead of the risk of a bad outcome (author would like to do this when it reduces the effect size). This is similar to using the risk of surviving instead of the risk of death. 99% survival may only be a 4% improvement over 95% survival, but most people would appreciate the 80% lower risk of death.
- suggesting that hospitalization time should be used for symptomatic recovery in a study where discharge is based on viral clearance (and only tested weekly).
- suggesting that a specific symptom such as cough should be used (author would prefer a less positive result for the study).
- suggesting that viral load is more important than symptomatic results.
- suggesting that mortality should be used in populations with zero mortality (for low-risk populations with no mortality, reduction in mortality is not possible, this does not mean a reduction in hospitalization, for example, is not valuable).
- suggesting that unadjusted results should be used in a study where the adjustments clearly make a significant difference (author wants to cherry-pick unadjusted cough results).
- suggesting that, for example, in a study of viral load where all patients recover, it is not valuable if treated patients recover faster (or are less likely to transmit the virus to others).
- suggesting that study selected outcomes should have priority rather than using a consistent pre-specified protocol, disregarding the added bias and the fact that this actually improves results for ivermectin (for example the very small event count negative serious outcomes in Krolewiecki, Vallejos, and Buonfrate would no longer have priority).
- suggesting that cough is a more important symptom than low SpO₂ or fever. Cough can persist for a long time after more serious symptoms resolve, and persistent cough may be caused by many conditions.
- suggesting that combined low dose treatment results should be used in a study that had a combined ivermectin/doxycycline arm (single dose ivermectin, 5 days doxycycline) and an ivermectin arm with treatment for 5 days.

We note that this personality has an extensive history of incorrect advice, including for example:

- claiming that flu is more dangerous than COVID-19
- claiming that SARS-CoV-2 is not airborne
- claiming that it's impossible to improve immune system functioning
- even believing and propagating a made up story that claimed ivermectin overdose was causing gunshot victims to wait at an ER

Author has taken a public position against early treatments for COVID-19 since at least July 2020. Given this longstanding and influential negative position, they may tend to view information with a negative filter and confirmation bias, and may be reluctant to admit errors. They acknowledge not having read all of the studies (and appear to have very superficially read others). They submitted zero feedback to us, suggesting that they know their comments are incorrect or that they have a motivation other than correcting errors. Author claims that they could not contact us, however there are over 50 feedback links throughout this article. We also note that the author is not open to critical feedback and routinely blocks Twitter users correcting mistakes or expressing anything critical on their feed. Reports suggest that the author also pre-emptively blocks people that have not even interacted with them, but are connected to other users reporting on their errors. Author acknowledges using a tool called MegaBlock that blocks all people that liked a specific tweet.

The author is also against vitamin D. Of the 82 vitamin D COVID-19 treatment studies, author suggests only one trial is worth looking at [\[Murai\]](#). This gives us a simple case to examine potential bias. [\[Murai\]](#) is a small trial providing no statistically significant effects (mortality $p = 0.43$, other outcomes are positive while also not significant). Author acknowledges that the trial is too small for a conclusion. More importantly, this trial provides no information about whether vitamin D reduces the risk of a serious COVID-19 case, because the patients in this trial already had a serious COVID-19 case (90% already on oxygen treatment at baseline). Author does not mention this. The trial also has poorly matched arms in terms of gender, ethnicity, hypertension, diabetes, and baseline ventilation, all favoring the control group. Further, this study uses an inappropriate form of vitamin D — cholecalciferol. In reality physicians would use calcifediol or calcitriol with late stage treatment, because they avoid a very long delay for conversion. We are unaware of a reason to use cholecalciferol in this case (other than to produce a null result). In summary, author's chosen study is the study providing the least useful information from the 82 studies to date, suggesting biased analysis.

Based on many comments, author appears to focus on superficial criteria such as typesetting and quality of writing. While many of the studies have been performed by non-native English speakers with minimal budgets, this does not imply the researchers are less reliable. Indeed, the author is highly critical of the program used to create a graph, for example, but is unable to see flaws in high budget high conflict of interest trials, even when they prompt >100 scientists to write an open letter requesting retraction [\[Open Letter\]](#).

Ten months later, the author has still not contacted us, making content-free comments on Twitter such as calling us "sh*tty". Other individuals pointing out errors with detailed and careful feedback get similar treatment, such as being called a "d*ckhead" and being blocked.

More details can be found in the [BBC response](#).

Scott Alexander response.

The analysis by SSC / Scott Alexander has a number of major issues.

Analysis with SSC's recommended exclusions can be found in the [supplementary data](#).

Update: after exclusions chosen by SSC, exclusions by GMK, excluding all late treatment, and excluding all prophylaxis studies, SSC found the results in Figure 29, showing statistically significant efficacy of ivermectin with $p = 0.04$. The method for computing this p value is not specified. We used the same event results and performed random-effects inverse variance DerSimonian and Laird meta analysis as shown in Figure 30, finding much higher significance with $p = 0.005$. We note that the effect extraction appears

biased against ivermectin, choosing the excessive dose arm in Buonfrate, and using the post-hoc exclusion in López-Medina. The Krolewiecki treatment count appears to have been scaled for the different group sizes. We do not know where SSC's Mahmud counts are from.

	Outcome	Placebo	Ivermectin	
Mahmud	Nonrecovery	120	89	
Ahmed	Fever nonrecovery	3	0	
Chaccour	Viral culture +	1	1	
Ravakirti	Death	4	0	
Bukhari	PCR-7+	25	4	
Mohan	Clinical worsening	5	3	
Lopez-Medina	Hospitalization	6	4	
Krolewiecki	PCR-5+	11	8	
Vallejos	Hospitalization	21	14	
Together	Death	95	86	
Buonfrate	Hospitalization	0	3	

Figure 29. SSC's analysis. SSC reports $p = 0.04$, with an unspecified method.

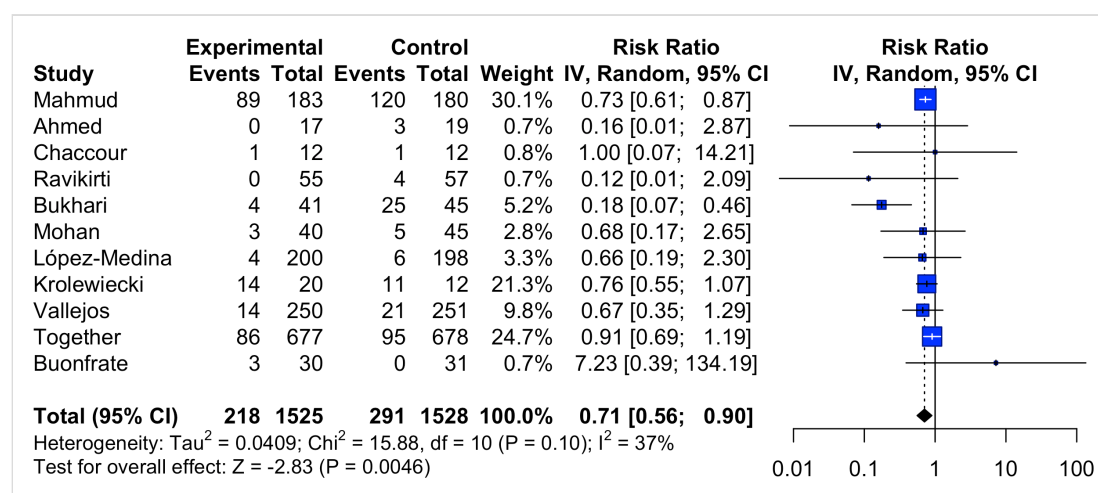


Figure 30. Random-effects meta analysis per SSC's chosen results, finding much higher significance.

Author appears to be against all treatments, labeling them all "unorthodox" and "controversial", even those approved by western health authorities, including casirivimab/imdevimab, bamlanivimab, sotrovimab, and paxlovid. **Update:** author's original article still refers to all treatments we follow as unorthodox and controversial, however they report that they actually recommend fluvoxamine, paxlovid, casirivimab/imdevimab, bamlanivimab/etesevimab, and sotrovimab, and suggest that they support all western health authority approved treatments which additionally includes remdesivir, budesonide, bebtelovimab, tixagevimab/cilgavimab, and molnupiravir. Author also has positive comments for zinc (but reports there is no proof). i.e., author appears to actually support at least 11 of the 42 treatments we follow. We note that the methodology is the same for all treatments.

We encourage the author to at least direct readers to government approved treatments, for which there are several in the author's country, and many more in other countries (including ivermectin). While approved treatments in a specific country may not be as effective (or as inexpensive) as current evidence-based protocols combining multiple treatments, they are better than dismissing everything as

"unorthodox". Elimination of COVID-19 is a race against viral evolution. No treatment, vaccine, or intervention is 100% available and effective for all variants — we need to embrace all safe and effective means.

The third-party analysis that author references for the strongyloides theory is confounded by treatment delay and dosage — the high prevalence group has more early treatment trials and a higher average dose, i.e., the analysis reflects the greater efficacy of early treatment and the greater efficacy of higher dosage. More details can be found in the [strongyloides](#) section.

Author refers to studies with positive but not statistically significant results as "negative" [Mohan], or "[the] original outcome would also have shown ivermectin not working" [López-Medina], which are incorrect conclusions [Amrhein]. **Update:** author believes this means we abandon statistical significance. We do not know where this comes from — all of our results report confidence intervals, and the first two words of this paper are "statistically significant". What is incorrect is making a negative conclusion based on an insignificant result. For example, if one study reports 50% lower mortality without reaching statistical significance, this does not mean that the treatment is useless. Consider if there are 10 studies all reporting ~50% lower mortality, the combined evidence may be strong even if each individual result is not statistically significant.

Author notes that: "if you say anything in favor of ivermectin you will be cast out of civilization and thrown into the circle of social hell reserved for Klan members and 1/6 insurrectionists", suggesting an environment that may bias the information that the author sees, and could unconsciously bias analysis. We note that similar environments influence the design, operation, and publication of some existing (and many upcoming) ivermectin trials.

Author looks at 29 of the 88 studies, which we note is much better than most commenters, but still ignores the majority of studies, including the prophylaxis studies.

The author finds efficacy at $p = 0.04$ in their analysis of 11 of the 29 studies they looked at. We note that simply looking at the other 59 studies will result in much higher confidence in efficacy. We also note that even at $p = 0.04$ with 11 independent studies, a rational risk-benefit analysis results in immediate adoption into protocols (pending stronger data with other combinations of treatments), and immediate collection of more data from sources without conflicts of interest.

However, ultimately the author at least partially supports the two prevailing theories that are commonly used by those against treatment. These theories require disregarding extensive contradictory evidence:

The steps required to accept the *no-significant-effect* outcome are extreme — one needs to find a reason to exclude most of the studies, disregard the strong treatment-delay response relationship, and disregard all prophylaxis studies. Even after this, the result is still positive, just not statistically significant. This does not support a negative recommendation. Widely accepted and effective (subject to dependence on viral variants) treatments like casirivimab/imdevimab, bamlanivimab, and sotrovimab were all approved without statistically significant mortality benefits.

The steps required to accept the *strongyloides-mechanism-only* conclusion are also extreme - we need to disregard the majority of outcomes occurring before steroid use, and disregard the strong treatment-delay response relationship which is contradictory. Figure 26 shows analysis by strongyloides prevalence. The third-party analysis referenced by the author is confounded by [treatment delay](#) and [dosage](#).

Author seems biased against believing any large effect size. We note that large effect sizes have been seen in several COVID-19 treatments approved by western health authorities, including paxlovid which the author is very positive about, and also that better results may be expected when studies combine multiple effective treatments with complementary mechanisms of action (as physicians that treat COVID-19 early typically do). *Update: author confirms this bias but appears to disregard it for paxlovid.*

Author is suspicious about a study based on the country of the researchers, and also appears biased against non-native speakers, with comments such as "*unreadable*" for one paper, compared to "*written up very nicely in real English*" for another. *Update: author confirms being biased against certain countries.*

Author calls a physician that has reported zero deaths and 5 hospitalizations with 2,400 COVID-19 patients "*a crazy person*" that "*put his patients on every weird medication he could think of*".

Author disregards the dramatically higher mortality for Gamma vs non-Gamma variants (aHR 4.73 [1.15-19.41] [*Zavascki*]), instead concluding that higher mortality indicates fraud in one instance, while in another instance assuming that the related confounding by time in the Together Trial is not significant.

Author's review of the 29 studies appears relatively cursory, for example author appears unaware that the ivermectin dosage is very different in the ivermectin + doxycycline arm of [*Ahmed*].

Author appears to accept the analysis and accusations of GMK as correct, however that author is often incorrect.

Author is concerned that we detail problems with [*López-Medina*], while correctly noting that the outcomes in this trial are actually positive and in favor of ivermectin (while not statistically significant in isolation).

Author is concerned that we specifically comment on [*López-Medina, Reis*]. We note that it has been others that have focused on these trials – we comment on them because they have received special attention, including being held up as sole evidence overriding all other trials, despite having major issues.

Author claims that nobody can find issues with [*Vallejos*], which suggests that they have not read the study, or our analysis.

AT response.

A technology blog published an article with incorrect and unsupported claims. The article refers to c19ivermectin.com (which is only a database of ivermectin research), but makes comments about this analysis. Most of the comments in this article are already addressed above.

Author correctly notes that the majority of results are positive and that no matter how you slice the data, the results are positive, but appears to dismiss the obvious reason without examining the evidence.

Author believes that because other effective treatments exist, and because we have also covered those, there must be a positive bias. For ivermectin though, we find evidence of a negative publication bias, and despite enormous worldwide attention, there is no evidence of missing negative trials, while there is substantial evidence of positive trials being delayed by editors (journals fast track null results, while holding positive trials and later returning them without review). We also note that many of the effective treatments are adopted by governments worldwide, including several in the author's country. Approved treatments include sotrovimab, casirivimab, imdevimab, bamlanivimab, etesevimab, budesonide, favipiravir, and convalescent plasma (although not showing efficacy in our analysis), others have already

been purchased pending approval or are not yet available (molnupiravir, proxalutamide), and others are widely accepted to be helpful, including in the author's country, despite gaining minimal attention from authorities (vitamin D, vitamin C) [Miller].

Author finds the heterogeneity in dosage, treatment time, etc. concerning. This heterogeneity is beneficial and gives us much more information on the situations where treatment is effective, and the optimal dosage. Results from a single study only apply to the conditions of that study and cannot be extrapolated to other conditions — author makes this mistake claiming another treatment is ineffective based on definitive evidence, but that evidence only applies to very late treatment in a very sick population with excessive dosage — not the optimal use of an antiviral for COVID-19. While we cannot use the larger evidence base to predict a specific situation, e.g., mortality in high risk patients with specific treatment delay and dosing, we can use the larger evidence base as evidence for/against efficacy, and many subgroup analyses have sufficient evidence for more specific cases.

Author refers to the withdrawn Elgazzar study (removed from this analysis on the same day) as a major development, however there was no significant change. Excluding 1 of 91 studies has very little effect, and the exclusion actually improves the treatment delay-response relationship. 55 of 88 studies need to be excluded to avoid finding statistically significant efficacy in a worst case sensitivity analysis.

Author is concerned that some studies use combined treatment, however 71 do not use combined treatment, and most of the additions are treatments independently known to not have significant efficacy alone.

We also note that the author has never contacted us.

How should the result be interpreted when pooling effects?

In the pooled analysis, the result is a weighted average of the improvement in the most serious outcome reported. The specific analyses should be used for specific outcomes. Note that a reduction in mortality logically follows from a reduction in hospitalization, which follows from a reduction in symptomatic cases, etc. Note that we have to consider all information to create the most accurate prediction of efficacy. While there are more sophisticated ways to combine all of the information, the advantage of the method used here is simplicity and transparency. Note that the highly significant results observed are without incorporating additional information that would further increase confidence, such as the treatment delay-response relationship.

Elgazzar.

This study was withdrawn and was removed from this analysis on the same day. There was no significant change (excluding 1 of 91 studies has very little effect, and the exclusion actually improves the treatment delay-response relationship).

Samaha.

This study was removed from this analysis within an hour of notification that it was pending retraction. There was no significant change in the results, and the exclusion improves the dose-response relationship.

Merino.

This preprint was censored by the original preprint host. Censors claim that the government treatment program, which used approved medications and saved over 500 people from hospitalization, was unethical. In part they also indicate that studies of "the effects of a medication on a disease outcome" are outside the scope of their site.

The author's response (not provided by the censors) can be found here: [\[twitter.com \(D\)\]](#). Author's provide the data and code for the study, and the results have been independently verified.

Angkasekwinai.

For [\[Angkasekwinai\]](#) see preliminary analysis at [\[c19ivermectin.com\]](#).

Pott-Junior.

This paper appears to have been censored at the request of the journal's founding editor [\[pubmed.ncbi.nlm.nih.gov\]](#). An external review is mentioned but is not provided, and there is no reply from the authors, or indication that the authors were notified. Conclusions in this study are limited due to the small size, however we should consider all information in the context of the full body of research.

Efimenko.

The conference publication for this analysis was self-censored by the authors, not due to any error in the analysis, but because authors believe ivermectin "has proven to be ineffective in clinical trials". This is incorrect, 56 studies show statistically significant positive results for one or more outcomes (30 prospective and 26 retrospective studies, including 21 Randomized Controlled Trials).

Carvallo.

Concerns have been raised about [\[Carvallo\]](#). There appears to be some valid concerns with potential data issues, and this study is excluded in the exclusion analysis. There is no significant change in results, with only a minor reduction in prophylaxis efficacy to 82% [68-89%]. However, it is difficult to trust information from the personality reporting the concerns. The author suggests that the study may not have happened at all, claiming for example that the team could not have afforded the medications without funding, and that a busy clinician would not have enough time. However, with just basic checks, the author would know that a drug company has confirmed donating the medications, that they confirmed authorization for the study was received, that the main hospital for the study requested additional supplies, and that the hospital confirmed ethics committee approval. For additional details see [\[O'Reilly\]](#). We also note that the combined treatment in this study has been independently shown to be effective, and the complementary mechanisms of action support improved efficacy of the combination [\[Figueroa\]](#).

Study Notes

For discussion of all studies see [c19ivermectin.com](#). A few studies have received special attention, with some considering them to be very strong evidence overriding the other 87 studies. We note limitations of these studies here.

Together Trial.

Many major issues including multiple impossible numbers, blinding failure, randomization failure, and many protocol violations, as detailed below. [Submit Updates or Corrections](#)

Also see: [Fraudulent Trial On Ivermectin Published By The World's Top Medical Journal.., Part 1, The False, Sinister, and Duplicitous Statements of the TOGETHER Ivermectin Trial Investigators](#), and [10 Questions for the TOGETHER Trial Investigators](#).

Private comments:

"There is a clear signal that IVM works in COVID patients.. that would be significant if more patients were added.. you will hear me retract previous statements where I had been previously negative" – Ed Mills, Together Trial co-principal investigator [[stevekirsch.substack.com](#)].

"I'm not interested in this question as its not the correct way to interpret the outcome" – Ed Mills, responding to a per-protocol death count request [[pierrekorv.substack.com](#)].

*"F*ck you" "F*ck off" "Glory to Satan" "You are one of these f*ckers.." "You f*cking *sshole"* – Ed Mills, responding to various emails on the trial and ivermectin research [[pierrekorv.substack.com](#)].

Public comments:

"There was no indication that ivermectin is clinically useful" – Ed Mills, Together Trial co-principal investigator.

"..the question of whether this study was stopped too early in light of the political ramifications of needing to demonstrate that the efficacy is really unimpressive.. really could be raised.." – Frank Harrell, "I totally agree with Frank" – Ed Mills [[vimeo.com](#)].

Severity	Issue (most recent update 19 days ago)	Author response
CRITICAL	1. Blinding failure	-
CRITICAL	2. Randomization violation, major confounding	-
CRITICAL	3. Data pledge violation, unavailable over 294 days from protocol, over 89 days from publication	-
CRITICAL	4. DSMC not independent	-
CRITICAL	5. Extreme conflicts of interest	-
CRITICAL	6. Three conflicting death counts	-
CRITICAL	7. Patient counts for reported period impossible	-
CRITICAL	8. Placebo arm counts vs. fluvoxamine arm not possible	-
CRITICAL	9. Conflicting adverse event counts	-
CRITICAL	10. 3-day dosing patients before March 23 missing (27 days ago)	-
CRITICAL	11. Multiple false statements by investigators (29 days ago)	-
CRITICAL	12. Investigators not responding to concerns (29 days ago)	-
CRITICAL	13. ICODA reports never having the data (19 days ago)	-
CRITICAL	14. Placebo tables may not match treatment tablets (19 days ago)	-
SERIOUS	15. Widespread community use of ivermectin	conflicting responses
SERIOUS	16. Team selected dose below what they believe is required	-
SERIOUS	17. Side-effect prevalence consistent with treatment error	-
SERIOUS	18. Screening to treatment delay unknown	-
SERIOUS	19. Unknown onset patients included	-

SERIOUS	20. <u>Conflicting comorbidity counts</u>	-
SERIOUS	21. <u>Unexplained >6 month delay</u>	-
SERIOUS	22. <u>Major imputation error</u>	-
SERIOUS	23. <u>Incorrect conclusion</u>	-
SERIOUS	24. <u>Missing age information</u>	-
SERIOUS	25. <u>Mid-trial protocol changes</u>	-
SERIOUS	26. <u>COI: designed by Cytel</u>	-
SERIOUS	27. <u>COI: analysis company works closely with Pfizer</u>	-
SERIOUS	28. <u>Unexpected differences in missing data</u>	-
SERIOUS	29. <u>Out of funding claim contradicted by funder (29 days ago)</u>	-
SERIOUS	30. <u>Misrepresentation of dosing recommendation (29 days ago)</u>	-
MAJOR	31. <u>Unknown onset results dramatically better</u>	-
MAJOR	32. <u>Mean delay likely excluding unknown onset</u>	-
MAJOR	33. <u>3-dose placebo much more effective</u>	-
MAJOR	34. <u>Multiple conflicting randomization protocols</u>	-
MAJOR	35. <u>Dominated by Gamma variant, no discussion</u>	-
MAJOR	36. <u>Viral load protocol violation, high Ct may hide efficacy</u>	-
MAJOR	37. <u>Conflicting dosing, previously unheard of weight limit</u>	-
MAJOR	38. <u>Conflicting target enrollment and reasons for termination</u>	-
MAJOR	39. <u>Soft primary outcome easy to game, selected after single dose arm</u>	-
MAJOR	40. <u>Conflicting futility thresholds, reported terminated due to futility, but threshold not reached</u>	-
MAJOR	41. <u>Subgroup analysis protocol violations</u>	-
MAJOR	42. <u>Many pre-specified outcomes missing</u>	-
MAJOR	43. <u>Single-dose recruiting continued after change</u>	-
MAJOR	44. <u>Funding list incorrect, missing Gates Foundation and Unitaid</u>	-
MAJOR	45. <u>Statistical analysis plan dated after trial start</u>	-
MAJOR	46. <u>Imputation protocol violation</u>	-
MAJOR	47. <u>Expected analyses missing</u>	-
MAJOR	48. <u>Single dose results missing</u>	-
MAJOR	49. <u>Conflicting reasons for dose change (27 days ago)</u>	-
MAJOR	50. <u>Details of placebo unspecified</u>	-
MAJOR	51. <u>Vaccine inclusion changes, likely confounding</u>	-
MAJOR	52. <u>Bayesian probability of superiority, featured for FLV, hidden in appendix</u>	-
MAJOR	53. <u>Two different per-protocol counts</u>	modified w/o explanation
UNKNOWN	54. <u>Source of ivermectin unspecified (fluvoxamine source specified)</u>	-
UNKNOWN	55. <u>100% adherence reported for 3-day placebo (29 days ago)</u>	-
MINOR	56. <u>Per-protocol conflict with fluvoxamine arm</u>	required by journal

Apr 5: The paper was silently updated, with no indication or explanation of the changes. Changes include: age range, placebo description, per-protocol count, and death counts (details below).

May 5: The paper was silently updated again. A new summary notes that authors *attempted* to screen for previous ivermectin use, contradicting both the discussion section, where authors claim they *ensured* no use for COVID-19, and the exclusion criteria and interview forms, which do not specify ivermectin use.

May 30 update: there is still no response to data requests, and the authors continue to maintain radio silence on the many serious issues [twitter.com (E)].

Delayed >6 months. The paper was delayed over 6 months with no explanation. The companion fluvoxamine arm, completed at the same time, was published Aug 23, 2021. The paper was submitted to NEJM in Sep 2021 [vimeo.com (B)]. COI forms suggest that additional authors were added after submission and the corresponding author changed from Prof. Mills to Dr. Rayner [doyourownresearch.substack.com], whose conflicts include Pfizer, Merck, the Gates Foundation, and the Australian Government.

No response to data request. The trial registration states that data was to be available at termination and upon request [clinicaltrials.gov (B)], however authors have not responded to a request for the data. Even funders of the trial have been unable to access the data [odysee.com]. Requests can be sent to thetogethertrial@gmail.com, let us know the outcome.

ICODA reports never having the data. Investigators report that the data is available via ICODEA: "The final trial dataset will be accessible by written request to the study principal investigators (G Reis or EJ Mills). There are no contractual agreements to limit access to final trial data. All data collected by the TOGETHER Trial will be shared with the International COVID-19 Data Alliance". Not only has there been no reports of successful access to the data, but an ICODEA manager reports that they have never had the data [t.me].

Placebo tablets may not match the treatment tablets. Authors do not specify the appearance of the placebo tablets, suggesting that they may not match the treatment tablets, providing an additional reason for blinding failure. A Brazilian investigator reports that, at the time of the trial, there was only one likely placebo manufacturer, and they reportedly did not receive a request to produce identical placebo tablets [doyourownresearch.substack.com (B)]. They also report that compounded ivermectin in Brazil is considered unreliable.

Three different death counts. In the original paper, Table 3 shows 21 and 24 deaths, while Table S6 shows 20 and 25 [twitter.com (F)]. In Table 3, death and grade 5 events showed the same 21/24 numbers, but different effect sizes, with 0.81 being closer to the 20/25 counts and the previously reported number. This is consistent with one death being moved between arms after manuscript generation, but not updated in Table S6 or the Table 3 AE RR. This cannot be explained by the safety population excluding patients with zero doses because the AE control deaths are higher. In email, a co-principal investigator suggested that the discrepancy was due to one being COVID-19 deaths and the other being all-cause deaths [stevekirsch.substack.com]. That explanation does not fit the data because one arm increases while the other arm decreases. Both co-principal investigators report in the paper that "they had full access to all the trial data and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol." A third set of death counts, 20 and 24, with RR 0.84, was presented by a co-principal investigator on Mar 18, 2022 [vimeo.com (C)]. In total, 4 different death relative risks have been presented: Mar 18, 2022 presentation: 0.84, Mar 30 paper: 0.88 (T3), 0.81 (T3 AE), and 0.80 (TS6, presented as 20 and 25 only without group sizes). 6 days after publication, the paper was updated, with

no information given on what was changed. In this version, a "respiratory, thoracic and mediastinal disorders" death was removed from the control arm and an "infections and infestations" death was added to the ivermectin arm. The paper still indicates RR 0.81 for death AE.

Trial was not blind. Ivermectin/placebo blinding was done by assigning a letter to each group that was only known to the pharmacist. If a patient received a 3-dose treatment, investigators immediately know that the patient is more likely to be in the treatment group than the control group, because 3-dose placebo was relatively rare (~46% from PP). If a patient received non-3-day treatment, investigators immediately know that the patient is not an ivermectin treatment patient. Moreover, by observing the frequency of allocations, investigators can easily determine which letter corresponds to active ivermectin 3-day treatment, thereby removing all blinding. For example, consider 3-dose-ivermectin and 3-dose-placebo being identified by the letters G and K. If allocations to date have been G:11 and K:20, there is a very high probability that K is ivermectin. Note that this blinding failure is only obvious because the journal required the authors to restrict to the 3-day placebo group. Also note that it would have been trivial to avoid if desired, for example by using a unique identifier for all medication bottles. Note that there may be additional reasons for blinding failure, for example the paper specifies identically shaped bottles, but does not appear to specify identical appearance tablets [doyourownresearch.substack.com (B)].

Patient counts do not match previously released enrollment graph. Authors claim the ivermectin and control patients were all from on or after March 23, 2021, however independent analyses of the enrollment graph (contained in this presentation [dcricollab.dcri.duke.edu]) require including patients prior to this date to reach the reported numbers [doyourownresearch.substack.com (C), longhaulwiki.com]. The enrollment graph shows much higher enrollement to ivermectin near the start of the trial. The only way that the number of placebo patients can be the same as the number of treatment patients is if placebo patients were taken from an earlier period [Marinos], which creates a nonconcurrent control group [nejm.org (B)] and substantial confounding by time as below.

Conflicting placebo arm counts across IVM/FLV arms. The IVM placebo arm has 679 patients and the FLV arm has 756. The 679 should be shared between the arms, with 77 extra patients for FLV. For FLV, there were 34 placebo patients requiring mechanical ventilation, for IVM there was only 25, indicating that 9 of the extra 77 placebo patients for FLV had mechanical ventilation, a much higher percentage during a period that had lower deaths and CFR (and included vaccinated patients). Placebo all-cause hospitalization shows 95/679 for IVM and 99/756 for FLV, i.e., only 4 of the extra 77 patients were hospitalized, but the paper reports an additional 9 patients with mechanical ventilation.

Fluvoxamine vs. Ivermectin Placebo Arm Comparison			
Fluvoxamine Placebo Arm		all-cause hospitalization 99/756 (Table 3) mechanical ventilation 34/756	
Jan 20, 2021		Aug 5, 2021	
Ivermectin Placebo Arm		all-cause hospitalization 95/679 (Table 3) mechanical ventilation 25/679	
Mar 23, 2021		Aug 6, 2021	
Extra patients for fluvoxamine placebo		DSMC met Aug 5 ending both arms, Aug 6 presentation shows 678 IVM placebo patients, possibly one placebo patient Aug 6.	
all-cause hospitalization 4/77 mechanical ventilation 9/77			
9 of the extra 77 patients had mechanical ventilation, while only 4 were hospitalized			

For FLV, there were 11 grade 1 AEs, for IVM there were 12, with 77 less patients.

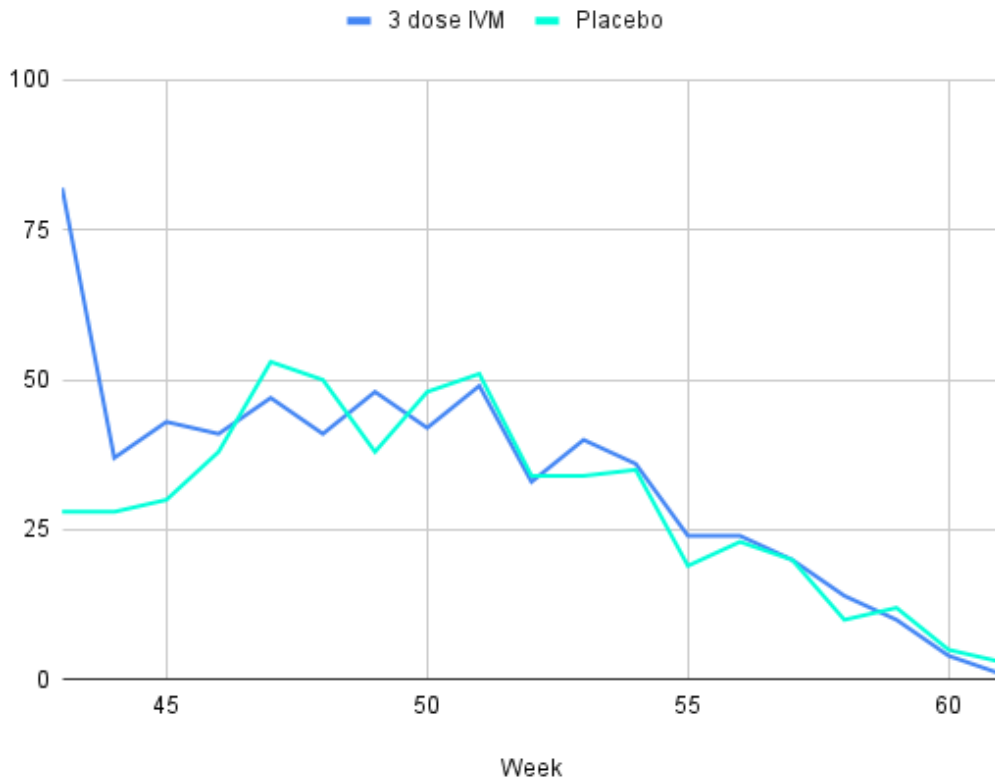
For FLV, there were 50 grade 3 AEs, for IVM there were also 50, meaning the 77 extra patients had 0% grade 3 AEs vs. an expected 7.4%

For FLV, there were 54 CKD patients according to Figure 3 and eTable1 (2 according to Table 1). For IVM there was 5.

DSMC not independent. Reviewer 1 of the protocol notes that the DSMC is not independent [gatesopenresearch.org]. Prof. Thorlund is Vice President of the contract research organisation (CRO, Cytel), professor at the sponsoring university, and an author of the protocol. Dr. Häggström is an employee of the CRO. [doyourownresearch.substack.com (C), twitter.com (G)] reveals many other conflicts. Prof. Thorlund has written >100 papers with Prof. Mills. Prof. Singh has written 29 papers with Prof. Mills. Prof. Orbinski has written 9 papers with Prof. Mills. The first version of the web site showed Prof. Mills and Prof. Thorlund as joint leads. Emails pointed to a company MTEK Sciences, founded by Prof. Mills and Prof. Thorlund (MTEK is hypothesized to stand for Mills, Thorlund, Edward, Kristian). MTEK received grants from the Gates Foundation. MTEK also employed Dr. Häggström. MTEK was acquired by Cytel in 2019. Dr. Häggström works for the Gates Foundation. Two members of the DSMC have published a paper with members of a well known anti-ivermectin research group [[Thorlund](#)] and Dr. Hill, whose meta analysis has reports of external influence [c19ivermectin.com (B), c19ivermectin.com (C), twitter.com (H)]. The trial protocol reports that "an independent DSMC will be established, composed of scientists of unrivalled reputation and expertise, without involvement with this research protocol."

Unequal randomization, significant confounding by time. The trial reports 1:1:1:1 randomization, however independent analysis shows much higher enrollment in the ivermectin treatment arm towards the start of the trial [c19ivermectin.com (D), longhaulwiki.com]. This introduces very significant confounding by time due to the major change in the distribution of variants. [[Zavascki](#)] show dramatically higher mortality for Gamma vs non-Gamma variants (28 day mortality from symptom onset aHR 4.73 [1.15-19.41]). Many more patients were randomized to ivermectin vs. placebo in the first few weeks, for example the first week shows 82 ivermectin vs. 28 placebo patients, 2.9x higher. The period of excess ivermectin enrollment coincides closely with a period of significantly higher deaths and CFR in Brazil.

Ivermectin vs. Placebo allocation



Moving-average case fatality rate of COVID-19

The case fatality rate (CFR) is the ratio between confirmed deaths and confirmed cases. Our rolling-average CFR is calculated as the ratio between the 7-day average number of deaths and the 7-day average number of cases 10 days earlier.

Our World in Data

LINEAR LOG



Source: Johns Hopkins University CSSE COVID-19 Data

CC BY

Missing time from onset patients show statistically significant efficacy. For the known time since onset subgroups, both groups show worse results than the overall results [twitter.com (I)], with the missing 317 patients showing significant efficacy RR 0.51, p = 0.02 (compared to 1.00 and 1.14 for known patients).

Unknown onset patients were enrolled, subgroup results opposite of previous trials. After imputation, the percentage of patients in the late treatment subgroup went from 46% to 56%. 87% of the unknown patients were predicted to be in the late group. This is reasonable and expected — patients that do not recall when the onset was are more likely to have had onset further in the past. What is not clear is how these patients could be enrolled in the trial, how many of these patients had onset >7 days, how this very late 317 patient subgroup could show much greater efficacy as above, and why authors did not report this result, analyze this in greater detail, or recommend further research.

Side effect profile consistent with many treatment patients not receiving authentic ivermectin and/or control patients receiving ivermectin. The side effects (e.g., gastrointestinal side effects were lower in the ivermectin arm) suggest that many ivermectin patients may not have received authentic ivermectin, or that placebo patients may have taken ivermectin. For comparison, there was a 3.6 times greater incidence of diarrhea in the treatment arm in [Lim].

A local Brazilian investigator reports that, at the time of the trial, there was only one likely placebo manufacturer, and they reportedly did not receive a request to produce identical placebo tablets [doyourownresearch.substack.com (B)]. They also report that compounded ivermectin in Brazil is considered unreliable. The protocol reports that "the study medication used will come from pharmaceutical plants that hold a commercial authorization for their production, already approved by ANVISA."

Vaccine inclusion changes. The trial changed from including vaccinated patients to excluding them on Mar 21, 2021 [clinicaltrials.gov (C), twitter.com (J)], and on Jul 5 the exclusion was changed to specify >14days. As above, meeting the reported placebo counts likely requires taking placebo patients from the earlier period, which has very significant confounding due to variant changes, and additionally confounding due to vaccination. Both of these favor the placebo group. The original vaccine inclusion criterion is unusual, but is shown in both the protocol and the clinicaltrials.gov record [clinicaltrials.gov (D), togethertrial.com]. This may have been chosen to reduce the potential for efficacy. For more on vaccination inclusion see [twitter.com (K)].

10. SARS-CoV2-vaccinated patients	10. Patient with stage IV chronic kidney disease or on dialysis.
11. Patient with stage IV chronic kidney disease or on dialysis.	11. Immunosuppressed patients / using corticosteroid therapy (equivalent to at least 10 mg of prednisone per day) and / or immunosuppressive therapy
12. Immunosuppressed patients / using corticosteroid therapy (equivalent to at least 10 mg of prednisone per day) and / or immunosuppressive therapy	12. Patients with a history of cancer in the last 05 years or undergoing treatment of a current cancer
13. Patients with a history of cancer in the last 05 years or undergoing treatment of a current cancer	13. Chronic renal disease KDIGO IV or End-Stage Renal Disease on chronic ambulatory renal replacement therapy
4. Patient with positive rapid test for SARS-CoV2 antigen performed on occasion of the screening or patient with a positive SARS-CoV2 diagnostic test within 07 days of the onset of symptoms.	4. Patient with positive rapid test for SARS-CoV2 antigen performed on occasion of the screening or patient with a positive SARS-CoV2 diagnostic test within 07 days of the onset of symptoms.
5. Willingness to use the proposed investigative treatment and follow the protocol-related procedures foreseen in the research	5. Willingness to use the proposed investigative treatment and follow the protocol-related procedures foreseen in the research
Exclusion Criteria:	Exclusion Criteria:
1. Negative SARS-CoV2 test.	1. Negative SARS-CoV2 test.
2. Flu-like symptom onset 08 days or more.	2. Flu-like symptom onset 08 days or more.
3. Patients with COVID-19 and hospitalization referral	3. Patients with COVID-19 being referred for hospitalization;
4. Patients with acute respiratory conditions due to other causes;	4. Patients with history of SARS-CoV-2 vaccine shot;
5. Dyspnea secondary to other acute and chronic respiratory causes or infections (eg:	

Incorrect conclusion. The conclusion states that ivermectin "did not result in a lower incidence of [hospitalization] or of [ER observation >6hr]". This is incorrect, hospitalization was 17% lower, which is not statistically significant with the sample size and typical statistical analysis. For the Bayesian analysis the authors use, the ITT probability of superiority for ivermectin was 79.4%, which is a positive result, the opposite of the conclusion.

Ivermectin use widespread in the community. Recent ivermectin use was not in the exclusion criteria. Ivermectin was available OTC, was recommended by the government for COVID-19, and had nine times higher sales [[twitter.com \(L\)](#)]. Authors claim they ensured patients did not use ivermectin via "extensive screening", but do not explain why this was not an exclusion criterion, or how this unwritten exclusion was ensured even though there is extensive missing data related to written exclusion criteria. Similar unwritten exclusions were not mentioned for other arms [[twitter.com \(M\)](#)], a primary investigator previously stated such an exclusion should not be an issue [[twitter.com \(N\)](#)], and it is not mentioned in the interview sheets [[osf.io](#)]. After publication, a co-principal investigator reportedly wrote that "even if some patients did access IVM, the fact that it is blinded should still maintain balance", which is incorrect, placebo patients taking ivermectin are expected to improve, treatment patients that already have significant tissue distributions may have positive, neutral, or negative responses to additional treatment.

Single-dose recruiting continued after change. The trial had requested moving to 3-dose treatment by Feb 15/19, when only 19 patients had been recruited, however the trial continued recruiting an additional 59 patients to single dose treatment [[twitter.com \(O\)](#)].

Per-protocol population different to the contemporary fluvoxamine arm. Table 2 per-protocol numbers show 92% per-protocol patients for ivermectin and only 42% for control. This appears to be a post-hoc change selecting only 3-day placebo patients, while similar selection does not appear to have been done for the companion fluvoxamine trial (showing 74% and 82% per-protocol patients for fluvoxamine and control) [[Reis \(B\)](#)].

Multiple conflicting randomization protocols. [[twitter.com \(P\)](#)] reviewed the randomization protocol, finding three different algorithms, and conflicting versions in the papers.

Time of onset, required for inclusion, missing for 317 patients. For the companion fluvoxamine arm, 24% of patients had an unknown time from onset, including 179 of the control patients [[Reis \(B\)](#)]. In this trial, 0 patients have an unspecified time from onset in Table 1, due to imputation. However, Figure 2 reveals that the time from onset is unknown for 317 patients, similar to the fluvoxamine paper. However, time from onset is required for the inclusion criteria. According to Figure 2, age and BMI also show missing values.

Conflicting comorbidity counts. The companion fluvoxamine arm ran from Jan 20 to Aug 5, 2021, while this trial ran from March 23 to Aug 6, 2021 — most control patients should be shared, with an additional 10% for fluvoxamine from the earlier start. The Aug 6 presentation, which has a date of 9:38am Aug 6 local trial time [[doyourownresearch.substack.com \(D\)](#)], shows 678 placebo patients, indicating that either 0 or 1 placebo patients were randomized on Aug 6. Zero patients should have been randomized on Aug 6, because authors cannot add patients after unblinding.

The fluvoxamine control arm shows 16/756 control patients with asthma. The ivermectin control arm has a subset of these patients (679), but shows a much higher prevalence of asthma (60 patients). This might be possible due to imputation if there was a very high percentage of missing data, however imputation does not appear to be a good explanation. For example, placebo CKD goes from 2 to 5 (FLV->IVM). First, it is not logical to impute CKD on patients based on the other variables. Second, the protocol specifies imputation only with up to 20% missing data, making it unlikely that imputation would add 150% of CKD patients. Third, the degree of change between FLV and IVM varies dramatically, with IVM reporting 666%, 275%, 150%, and 43% more patients for CPD, asthma, CKD, and CCD, without any clear explanation for similar differences in the percentage of missing data (all were collected on the same interview form).

Conflicting target enrollment. There are conflicting target enrollment numbers. The protocol showed 800 patients per arm as of Mar 21, 2021 (after the trial started) [[static1.squarespace.com](#), [twitter.com \(Q\)](#)], the co-principal investigator reported 800 per arm in an interview published June 14, 2021

[halifaxexaminer.ca], and the protocol changed to 681 on June 22 [static1.squarespace.com (B)]. However, the trial record from Jan indicates 2724 (681*4) patients [clinicaltrials.gov (D)], suggesting that the 800 goal was later, and was kept for fluvoxamine but reverted for ivermectin. The fluvoxamine arm which started two months earlier was terminated at the same time, and was terminated due to superiority [Reis (B)] after 741/756 patients. Note that Gamma was declining significantly around the termination point, which likely favors improved efficacy if the trial continued, given the late treatment and dosage used. The co-principal investigator reports three different reasons for stopping the trial [twitter.com (R)]: a) because they ran out of money, b) because third parties were not supportive, and c) it was done by the DSMC and was out of their control.

Reportedly terminated for futility although futility threshold not reached. The trial was reportedly terminated due to futility [twitter.com (S)], however the futility thresholds were 20%, 40% and 60%, and all published probabilities are >60% (ITT 79.4%). Additionally, the fluvoxamine arm did not have the higher 60% threshold, only using 40%. Note the DSMC was not independent as below.

Screening to treatment delay. Most Together Trial protocols show an additional day delay in already late treatment for most patients. The Aug 5, 2021 protocol published with the metformin paper [ars.els-cdn.com], shows treatment administration one day after screening, baseline, and randomization (Table 2, schedule of study activities). This can also be found in the protocol dated Mar 11, 2021 [drive.google.com (C)]. The protocol attached to the ivermectin paper, dated Feb 15, 2021, shows a different schedule, stating that the treatment *should* be administered on the same day of randomization. There is no explanation of when this change was made, how the overlapping metformin and ivermectin arms could use different schedules, or how this change was implemented (there are many tasks in the screening and baseline visits). There is no reporting for how many patients received treatment on the same day. The form for the first treatment visit asks if there were clinical events including >6hr ER visits since the baseline visit, which would not be possible if this visit was immediately after randomization. Time of first treatment was recorded [osf.io], but no information has been reported. According to [Forrest], WhatsApp messaging and video was used for recruitment, raising the question of how medication was delivered in cases where recruitment was done online.

	Screening Visit (D-0)	Baseline and Randomization (1) D-0	Day 1
Informed Consent	X		
SARS-CoV-2 Rapid Test	X ⁽¹⁾		
Eligibility Criteria Review	X ⁽²⁾		
Pregnancy Test	X ⁽³⁾		
Demographics	X ⁽⁵⁾		
Co-morbidities and Risk Factors	X		
Medical History	X		
WHO Clinical Worsening Scale	X		X
Exposure to Index Case Information		X	
Substance Abuse		X	
PROMIS Global Health Scale		X ⁽⁶⁾	
ECG		X	
Height and Weight		X	
Nasopharyngeal Swab		X	
Randomization		X	
Concomitant Medications		X	X
Investigational Treatment Administration			X ⁽⁷⁾

Mean delay. The reported mean number of days from symptoms to randomization likely only includes known onset patients and therefore is likely to significantly underestimate the actual average, in addition to not including the time between randomization and treatment.

Viral load not reported. The protocol has change in viral load as an outcome, however only viral clearance is reported, and without any details (for example, using a high Ct value would have limited relevance).

Incorrect dose reporting, many patients at higher risk due to BMI may have received lower per kg doses, and show lower efficacy. The paper reports 400µg/kg for 3 days, however the protocol indicates that this was only up to 90kg, meaning that the dose received for higher-risk high BMI patients was even further reduced from dosage which is already far below clinician recommendations for the dominant variant [twitter.com (T)]. 50% of patients had BMI ≥30. Much greater efficacy was seen in the low BMI subgroup (RR 0.77 vs 0.98).

Plasma concentration below known effective value. [Krolewiecki] show an antiviral effect only with plasma concentrations above 160ng/mL. Figure S5 shows that the authors expected the mean concentration to be well below this level [twitter.com (U)]. Dosage requirements are likely to vary significantly depending on many factors including the variant encountered, time of administration, mode of administration, patient genetics, concomitant medications, SOC, and the distribution of the infection in different tissues. However, the dose used is far below what is recommended by clinicians for post-infection treatment with the Gamma variant — about 2.5 - 6.5x lower, depending on the recommendation and which estimate of fasting/fed administration is used. The trial used fasting administration, however Merck's product information reports that "administration of 30mg ivermectin following a highfat meal resulted in an approximate 2.5-fold increase in bioavailability relative to administration of 30mg ivermectin in the fasted state." [merck.com]. Moreover Dr. Craig Rayner, a senior investigator on the trial, previously published research indicating that a higher dose is required [sciencedirect.com], raising the question of why the dose and fasting administration was chosen, especially for the initial single dose regimen.

Primary outcome easy to game, selected after ivermectin one dose arm. The subjective "emergency room visit for >6 hours" criterion shows higher risk (RR 1.16), while hospitalization is lower (RR 0.83 all-cause, RR 0.84 COVID-19). The primary outcome results were set on March 21, 2021, after the single dose ivermectin arm. Given the known public biases of some investigators, this may have been specifically chosen to reduce efficacy. Authors claim that the 6hr threshold did not include waiting time, however the emergency visit form has no mention of waiting time, only recording presentation and discharge times [osf.io].

Including contraindicated chronic kidney disease patients. "Stage IV chronic kidney disease or on dialysis" was an inclusion criterion, however ivermectin is contraindicated with kidney disease [Arise, en.wikipedia.org, Nunes] (not always recognized, and may be less critical with very low dose use for other conditions). According to Table 1 there were only 7 CKD patients, however two conflicting numbers are provided in the fluvoxamine paper [Reis (B)]: Table 1 reports 2 CKD placebo patients - it's not clear how CKD was imputed for 3 more patients in the smaller IVM group. Moreover, Figure 3 shows 54 placebo CKD patients for FLV.

Antigen test requirement. The protocol indicates that patients with a negative test may be included if they become positive a few days later, potentially resulting in a long unreported delay between randomization and treatment, depending on how investigators interpreted the protocol. The requirement for a positive antigen test excludes the possibility of early treatment in many cases - tests have very high false negative rates in the early stages of infection, and symptoms may appear before the test becomes positive.

Inconsistent subgroup analysis. The presented subgroup analysis is inconsistent with plans and with the fluvoxamine paper, including not presenting pre-specified subgroups, presenting subgroups that were not pre-specified, presenting different subgroups to the contemporary fluvoxamine paper, and modifying subgroup definitions [twitter.com (V)].

Missing analysis. Authors do not provide time from onset analysis for either mortality or hospitalization, only the combined measure including the ER visits where anomalous results are seen. Authors do not provide per-protocol or mITT results for mortality or hospitalization. Per-protocol mortality results were provided for the companion fluvoxamine trial.

Missing outcomes. Many outcomes specified in the protocol appear to be missing, including the co-primary outcome of COVID-19 mortality (only all-cause mortality is provided, specific AE details not provided), time to clinical failure, days with respiratory symptoms, mortality due to pulmonary complications, cardiovascular mortality, COVID-19 symptom scale assessment, WHO clinical worsening scale assessment, and 14 day mortality.

Imputation error. In the paper authors use imputation in Table 1 but not in Figure 2. Authors also released a version of Figure 2 with imputation [togethertrial.com (B)], where the numbers for age and BMI now match the imputed numbers in Table 1. However, the time from onset numbers are very different, with the treatment arm showing 302 patients for 0-3 days, and the imputed version of Figure 2 showing 367 [doyourownresearch.substack.com (E)].

Missing age information. According to Figure 2, 98 patients are missing age information [twitter.com (W)].

Out of funding claim contradicted by funder. A co-principal investigator has reported that the trial was stopped because they ran out of funding, however this is contradicted by the Rainwater Foundation, which reported that they would have given more money to finish the trial if the investigators had asked [pierrekoru.substack.com (B)].

Misrepresentation of dosing recommendation. Investigators have misrepresented an email from the FLCCC regarding recommended dosing [[pierre.kory.substack.com \(B\)](#)].

Unexpected differences in missing data. Age is unknown for 98 patients, however according to Figure 2, BMI is missing for only 11 patients, smoking status is unknown for only 2 patients, lung disease is unknown for only one patient, and cardiovascular disease is known for all patients.

Mid-trial protocol changes. There were several mid-trial protocol changes on July 5, 2021 [[clinicaltrials.gov \(E\)](#)]. The number of patients for viral load analysis was reduced, only for the ivermectin arm. All-cause, cardiovascular, and respiratory death outcomes were deleted (all-cause was reported). Exclusions were modified to allow enrolling patients vaccinated within the last 14 days. Inclusion criteria were modified to allow enrolling healthy young people – the criterion “fever >38C at baseline” was added, allowing enrollment independent of increased risk.

Statistical analysis plan dated after trial start. The statistical analysis plan appears to be dated after the trial started [[twitter.com \(X\)](#)].

Per-protocol placebo results very different. The 3-dose placebo appears to have been much more effective [[Marinos, twitter.com \(Y\)](#)]. This could be consistent with placebo patients accidentally receiving treatment.

Imputation protocol violation. The protocol specifies multiple imputation with up to 20% of missing data, however imputation was done with time from symptom onset, which has >23% missing data [[twitter.com \(Z\)](#)].

Two different per-protocol counts. Figure 1 shows 228 per-protocol for the control arm, while Table 2 shows 288. This was modified in the Apr 5 update without explanation.

Conflicting adverse event counts. Table 3 and Table S6 adverse event counts do not match for any grade, e.g., grade 1/2 in Table S6 shows 82 for IVM, while Table 3 shows 65 [[twitter.com \(AA\)](#)]. The Apr 5 update changed the grade 5 events without explanation, however the other grades remain conflicting.

3-day dosing patients before March 23 missing. The co-principal investigator wrote on March 6 that 3-day dosing was being administered, and that the clinicaltrials entry was out of date at that time [[twitter.com \(AB\)](#)]. This earlier start of the 3-dose arm would resolve an outstanding major inconsistency. Analysis of the trial randomization shows that reaching the 3-day placebo count requires patients from March 4 [[doyourownresearch.substack.com \(F\)](#)], and it would be logical for the 3-day placebo and 3-day active arms to have started on the same day. This reinforces existing concerns as to which patients were included in the analysis, and adds additional questions regarding what happened to the patients prior to March 23, and if patients were treated prior to ethics approval. Ethics approval for the dose change was received on March 21 according to the paper [[twitter.com \(AC\)](#)], with the regulator document dated March 15 [[twitter.com \(AD\)](#)].

Multiple false statements by investigators. There has been multiple false statements by investigators raising questions about their ethics and the reliability of their work [[pierre.kory.substack.com](#)].

Investigators not responding to concerns. After details of major data errors and protocol violations became known, investigators appear to have stopped responding to all researchers regarding serious concerns with the trial [[pierre.kory.substack.com, twitter.com \(E\)](#)] (and have still not responded to us).

Possibly the largest financial conflict of interest of any trial to date. Disclosed conflicts of interest include: Pfizer, Merck, Bill & Melinda Gates Foundation, Australian Government, Medicines Development for Global Health, Novaquest, Regeneron, Astrazeneca, Daichi Sankyo, Commonwealth Science and Research Organization, and Card Research. Many conflicts of interest appear unreported. For example, Unitaid is a sponsor [*Harper, togethertrial.com (C)*].

Analysis done by a company that receives payment from and works closely with Pfizer. All analyses were done by Cytel. Cytel is a statistical modelling company that helps pharmaceutical companies get approval – they work very closely with Pfizer [*cytel.com (B)*]. Cytel's software and services are used by the top 30 pharmaceutical companies [*cytel.com (B)*].

A co-principal investigator works for Cytel and the Gates Foundation [*empendium.com*]: "The majority of the time I work for a company called Cytel, where I design clinical trials, predominantly for the Bill & Melinda Gates Foundation".

Reportedly, the first author's center is funded by pharmaceutical companies, and independent investigators tried to participate in the trial but were denied [*odysee.com (B)*].

The Gates Foundation is a founding partner of GAVI, which took out Google ads telling people not to use ivermectin [*twitter.com (AE)*], and a major funder of Unitaid, which may have modified the results of the Hill meta analysis in a way that prevented adoption [*c19ivermectin.com (B)*, *c19ivermectin.com (C)*, *twitter.com (H)*].

Associated with MMS Holdings. The trial is associated with MMS Holdings [*dcricollab.dcri.duke.edu*], whose mission includes helping pharmaceutical companies get approval and designing scientific studies that help them get approval. One of their clients is Pfizer [*mmsholdings.com*].

Certara. One of the senior investigators was Dr. Craig Rayner, President of Integrated Drug Development at Certara - another company with a similar mission to MMS Holdings. They state on their website that: "Since 2014, our customers have received over 90% of new drug and biologic approvals by the FDA." One of their clients is Pfizer [*certara.com*].

Local variant shows very different characteristics. The trial took place in an area of Brazil where the Gamma variant was prominent. Brazilian clinicians report that this variant is much more virulent, and that significantly higher dosage and/or earlier treatment is required, as may be expected for variants where the peak viral load is significantly higher and/or reached earlier [*Faria, Nonaka*].

Funding list incorrect. The paper does not include the Bill and Melinda Gates Foundation or Unitaid as funders, however the protocol shows the Gates Foundation [*gatesopenresearch.org (B)*] and the web site shows Unitaid [*togethertrial.com (C)*].

Single dose arm results missing. Results for the single dose ivermectin arm have not been reported.

Anomalous results from the same region. A local Brazilian investigator reports that the study was conducted in almost the same time and location as the Brazilian component of the molnupiravir trial. Notably, molnupiravir's EUA relied on the unusually higher efficacy observed in Brazil.

Designed by Cytel. The trial was designed by Cytel, a company that helps pharmaceutical companies get approval and that works very closely with Pfizer [*cytel.com, cytel.com (C)*]. Cytel's software and services are used by the top 30 pharmaceutical companies [*cytel.com (B)*].

Bayesian probability of superiority hidden in appendix. The bayesian probability of superiority figure, featured in the main paper for FLV, MET, HCQ, was hidden in the appendix for IVM [[twitter.com \(AF\)](#)].

Conflicting reasons for dose change. Conflicting reasons have been given for the change from 1-day to 3-day dosing. In email from March 6, the co-principal investigator says the change was "based on emerging trials from Andrew Hill's synthesis" [[twitter.com \(AG\)](#)]. The paper says the change was made "on the basis of feedback from advocacy groups". Neither of these match the report that the dosing change was made at the request of one of the trial funders [[pierre.kory.substack.com](#)].

Placebo unspecified. The placebo appears to be unspecified in the paper and protocol. The initial trial announcement indicated the placebo was vitamin C [[cytel.com \(C\)](#)], which would be an active treatment according to the [results of 45 studies](#) (mortality RR 0.72 [0.59-0.88]). The metformin arm reports using talc, however fluvoxamine and ivermectin do not appear to report details of the placebo, which could potentially be different, for example based on manufacturer limitations for matching active treatment tablets.

Previous protocol changes. There are two previous published protocols, both are called "version 1", we refer to them as 1A (3/11/21 [[drive.google.com \(C\)](#)]) and 1B (8/5/21 [[gatesopenresearch.org](#)]). 1B deletes subgroup analysis by treatment delay, and deletes a statement requiring prior approval for amendments. 1B adds the statement: "we hypothesize that younger patients will benefit more than older patients."

Patients 50 years old were assigned to different groups in Table 1 and Figure 2 (≤ 50 vs. < 50).

Greater efficacy was seen for patients > 50 (RR 0.77) vs. patients ≤ 50 (RR 1.01).

Source of ivermectin unspecified. Authors do not specify the source of the ivermectin used in the trial, whereas they do specify the source for the fluvoxamine arm (Luvox, Abbott). Depending on the source, Ivermectin has been reported to be of unreliable quality in Brazil.

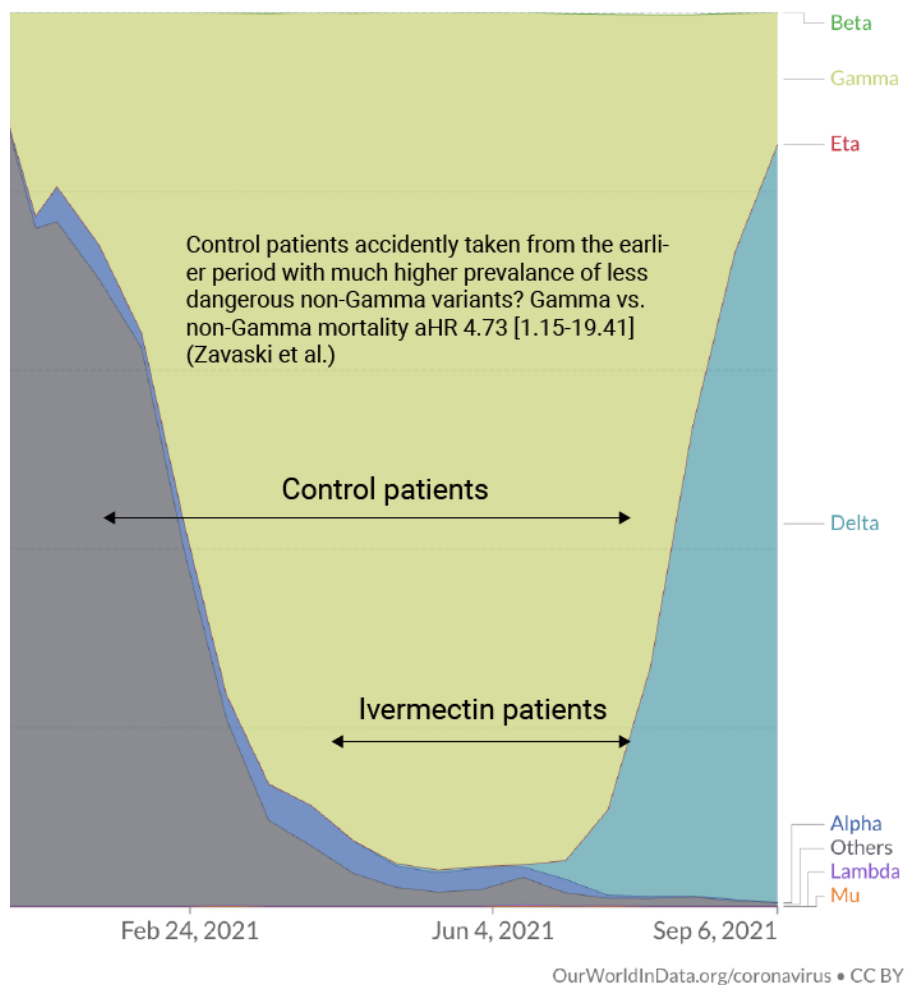
100% adherence reported for 3-day placebo. Reported numbers indicate that there was 100% adherence among 288 patients assigned to 3-day placebo, which is unexpected [[doyourownresearch.substack.com \(F\)](#), [pierre.kory.substack.com](#)].

The following comments are prior to the publication. We note that authors claim they have not included patients prior to the time period for the 3 dose ivermectin patients, however this conflicts with previously reported data as per the analyses above.

The trial randomization chart does not match the protocol, suggesting major problems and indicating substantial confounding by time. For example, trial week 43, the first week for 3 dose ivermectin, shows ~3x patients assigned to ivermectin vs. placebo [[reddit.com](#)]. Treatment efficacy can vary significantly over time, for example due to overall improvement in protocols, changes in the distribution of variants, or changes in public awareness and treatment delays. [[Zavascki](#)] show dramatically higher mortality for Gamma vs non-Gamma variants (28 day mortality from symptom onset aHR 4.73 [1.15-19.41]), and the prevalence of the Gamma variant varied dramatically throughout the trial [[ourworldindata.org](#)]. This introduces confounding by time, which is common in COVID-19 retrospective studies and has often obscured efficacy (many retrospectives have more patients in the treatment group earlier in time when overall treatment protocols were significantly worse).

According to this analysis [[reddit.com](#)], the total number of patients for the ivermectin and placebo groups do not appear to match the totals in the presentation (the numbers for the fluvoxamine arm match) — reaching the number reported for ivermectin would require including some of the patients

assigned to single dose ivermectin. Reaching the placebo number requires including placebo patients from the much earlier ivermectin single dose period, and from the early two week period when zero ivermectin patients were assigned. If these earlier participants were accidentally included in the control group, this would dramatically change the results in favor of the control group according to the changes in Gamma variant prevalence.



An investigator from Brazil notes that the gamma variant became prevailing in the state of Minas Gerais later than in the rest of the country, with the time when gamma prevailed for the trial locations being more closely aligned with the start of the ivermectin arm [[ufmg.br](#)]. Due to the substantial differences in disease course and risk between the variants, authors need to consider only patients recruited during the same time period.

Treatment delay is currently unknown, however the protocol allows very late inclusion and a companion trial reported mostly late treatment. Overall mortality is high for 18+ outpatients. Results may be impacted by late treatment, poor SOC, and may be specific to local variants [[Faria](#), [Nonaka](#), [Sabino](#)]. Treatment was administered on an empty stomach, greatly reducing expected tissue concentration [[Guzzo](#)] and making the effective dose about 1/5th of current clinical practice. The trial was conducted in Minas Gerais, Brazil which had substantial community use of ivermectin [[otempo.com.br](#)], and prior use of ivermectin is not listed in the exclusion criteria.

This trial uses a soft primary outcome, easily subject to bias and event inflation in both arms (e.g., observe >6 hours independent of indication). There is also an unusual inclusion criteria: "patients with expected hospital stays of ≤ 5 days". This is similar to "patients less likely to need treatment beyond SOC to recover", and would make it very easy to reduce the effect seen. This is not in either of the published protocols.

RCTs have a fundamental bias against finding an effect for interventions that are widely available — patients that believe they need treatment are more likely to decline participation and take the intervention [Yeh], i.e. RCTs are more likely to enroll low-risk participants that do not need treatment to recover (this does not apply to the typical pharmaceutical trial of a new drug that is otherwise unavailable). This trial was run in a community where ivermectin is widely known and used.

The same trial's results for a previous treatment were initially reported as RR 1.0 [0.45-2.21] [ajtmh.org], while the final paper reported something very different — HR 0.76 [0.30-1.88] [jamanetwork.com].

Trial design, analysis, and presentation, along with previous public and private statements suggest investigator bias. Design: including very late treatment, additional day before administration, operation in a region with high community use, specifying administration on an empty stomach, limiting treatment to 3 days, using soft inclusion criterion and a soft primary outcome, easily subject to bias. Analysis: authors perform analysis excluding events very shortly after randomization for fluvoxamine but not ivermectin, and report viral load results for fluvoxamine but not ivermectin. Presentation: falsely describing positive but not statistically significant effects as "no effect, what so ever" [Amrhein, odysee.com (C)]. Prior statements: [odysee.com (C)].

The local Brazilian investigator also reports that nitazoxanide was tested in the same location, however very few patients reportedly experienced urine discoloration, while 100% are expected to experience this side effect; and that 6-hour observation is a poor choice because it is almost impossible to stay less than 6 hours in Brazil.

For additional issues see: [covid19criticalcare.com, doyourownresearch.substack.com (G), longhaulwiki.com, Marinos, Marinos (B), stevekirsch.substack.com, trialsitenews.com (C), twitter.com (AH), twitter.com (AI), twitter.com (AJ), twitter.com (AK)]. Protocols, approvals, and statistical analysis plans can be found here [togethertrial.com (D)].

NCT04727424.

ACTIV-6.

RCT low-risk outpatients with very late treatment (median 6 days, 25% ≥ 8 days) in the USA, showing 98% probability of efficacy for clinical progression at day 14, a treatment delay-response relationship, and significant efficacy for patients with severe symptoms at baseline. Efficacy was higher over calendar time, which may reflect higher efficacy with more recent variants. Efficacy was higher for vaccinated patients.

Design, presentation, and analysis shows a strong negative bias. While authors recommend and are performing further study, notably they are continuing with most flaws including a design focusing on very late monotherapy, while extensive research shows that early treatment is critical for antivirals, and a growing body of research shows greater and synergistic benefits from polytherapy protocols commonly used by physicians that treat COVID-19. [Submit Updates or Corrections](#)

There are many major issues as below.

Severity	Issue (most recent update 12 days ago)	Author response
CRITICAL	1. Superiority found, not reported (13 days ago)	-
CRITICAL	2. Very late treatment	-
CRITICAL	3. Primary outcome not reported, closest reported outcome shows superiority of ivermectin (13 days ago)	-
CRITICAL	4. Patients with symptoms >7 days included	-
CRITICAL	5. No response to data request (14 days ago)	-
CRITICAL	6. Outcomes reported do not match protocol (13 days ago)	-
CRITICAL	7. No COVID-19 mortality/hospitalization reported (14 days ago)	-
CRITICAL	8. Many pre-specified outcomes missing (12 days ago)	-
CRITICAL	9. Protocol unavailable (13 days ago)	-
CRITICAL	10. IDMC not independent (12 days ago)	-
CRITICAL	11. Reported primary outcome low relevance (13 days ago)	-
CRITICAL	12. Shipping and PCR delays largely enforce late treatment	-
CRITICAL	13. Blinding failure	-
CRITICAL	14. Extreme conflicts of interest	-
CRITICAL	15. Treatment delay-response relationship	-
CRITICAL	16. Asymptomatic patients included	-
CRITICAL	17. Disingenuous conclusion (14 days ago)	-
CRITICAL	18. Up to 6 days shipping delay (14 days ago)	-
SERIOUS	19. Randomization failure (15 days ago)	-
SERIOUS	20. Low risk patients (14 days ago)	-
SERIOUS	21. No adherence data (14 days ago)	-
SERIOUS	22. Subject to participant fraud (13 days ago)	-
SERIOUS	23. Not enough tablets provided	-
SERIOUS	24. Monotherapy with no SOC for most patients	-
SERIOUS	25. Over 2x greater severe dyspnea at baseline for ivermectin	-
SERIOUS	26. Authors suggest high-income country healthcare is better, however almost all patients received no active SOC	-
SERIOUS	27. Placebo unspecified	-
SERIOUS	28. No breakdown of severe outcomes	-
MAJOR	29. No subgroup counts for treatment delay	-
MAJOR	30. Skeptical prior not justified (12 days ago)	-

Superiority found, not reported. Both day 7 and day 14 clinical progression results show superiority of ivermectin. The protocol states: "*The Study Drug is found to have benefit (efficacy): A posterior probability of meaningful benefit (e.g. OR < 0.9) for a study drug in comparison to the placebo control of > 0.95 will result in a declaration of overall superiority*" [fnihi.org].

Primary outcome not reported, closest reported outcome shows superiority of ivermectin. The protocol shows the primary outcome using a longitudinal statistical model with an ordinal variable based on symptom count and hospitalization/death measured daily until day 14 [fnihi.org]. This outcome is not

reported. The closest reported outcome is clinical progression at 14 days, which shows superiority of ivermectin, OR 0.73 [0.52-0.98], posterior probability of efficacy 98%, exceeding the pre-specified threshold.

Very late treatment. Patients were treated a median of 6 days late, with 25+% 8+ days late. Extensive research for COVID-19 and other viral diseases show that early antiviral treatment is critical. While authors recommend (and are performing) further study, they do not recommend or perform the obvious step of doing an early treatment trial, as is done for NIH recommended treatments like Paxlovid, suggesting a strong negative bias with a goal of maintaining late treatment and obtaining poor results.

Outcomes reported do not match protocol. The reported outcomes are very different to the trial registration [clinicaltrials.gov (F)] and the protocol [fnihi.org]. The trial registration shows three primary outcomes, of which zero are reported in the paper. The protocol shows the primary outcome using a longitudinal statistical model with an ordinal variable based on symptom count and hospitalization/death measured daily until day 14.

No response to data request. Authors have not responded to a request for the data.

No COVID-19 mortality/hospitalization reported. Authors only report all-cause mortality and hospitalization. Notably, the baseline hospitalization and mortality rate for non-COVID-19 causes may account for the death and many of the hospitalizations. This may also explain why authors report only 28 day mortality/hospitalization in violation of the protocol where the primary outcomes specify 14 days [clinicaltrials.gov (F)]. Additionally, adverse events show only one case of aggravated COVID-19 pneumonia for ivermectin, versus 3 for placebo.

Many pre-specified outcomes missing. Authors do not report [fnihi.org]:

- OR describing the overall difference in symptoms and clinical events over 14 days (primary outcome)
- Overall clinical progression OR (only specific day 7, 14, 28 values are provided)
- Time to first urgent care, emergency care, hospitalization or death
- Risk and time to event for each component of the composite
- Mean and median time to symptom freedom
- Overall QOL OR
- Day 7, 14, 28, 90 QOL OR
- Mean difference in QOL scores at day 7, 14, 28, 90
- Mean and median time to symptom resolution (only a new sustained resolution measure is reported, which is not in the protocol)
- Day 90 mean and median symptom count

Protocol unavailable. No detailed protocol is available. For example, the Bayesian threshold for significance is not known and appears to be withheld. A typical posterior efficacy threshold of 97.6% is met by the clinical progression on the ordinal outcome scale at day 14, OR 0.73 [0.52-0.98] 0.98. Notably, the discussion includes vague and arbitrary "clinical relevance" and "substantial clinical benefit" rather than statistical significance. *Update: partial protocol located [fnihi.org], threshold was exceeded. The protocol appendix is still unavailable which includes contraindications, exclusions, formulation, appearance, packaging, dispensing, dosing, and dose rationale.*

Reported primary outcome low relevance. The reported primary outcome (which matches neither the trial registration or the protocol) is of relatively low relevance being based on sustained absence of all symptoms, where symptoms includes many things that may be found after viral clearance and may be unrelated to COVID-19, including fatigue, headache, and cough (which may remain for some time). Authors may have searched for the outcome that shows the least benefit. The 3-day sustained definition further adds two days for all participants, reducing efficacy. Authors should report data for more significant symptoms such as dyspnea, fever, and loss of sense of taste/smell.

Patients with symptoms >7 days included. The trial specifies symptoms ≤ 7 days, however subgroup results show symptoms $\leq 9, 11$, and 13 days, and the Q3 for the ivermectin arm was 8 days, indicating 25% of patients with a treatment delay of ≥ 8 days. The difference is likely due to the authors not considering receipt of medication or treatment time in inclusion, i.e., due to shipping delays. However, ≤ 7 days treatment delay already makes the results inapplicable to real-world usage where antivirals are used early.

Asymptomatic patients included. Study inclusion required >2 symptoms, however the subgroup analysis includes 109 patients with no symptoms, where results favored placebo. The primary outcome may reach statistical significance without these patients.

Shipping and PCR delays largely enforce late treatment. Authors required positive PCR before randomization, and shipped medication to participants. The delay before PCR results become positive, delay in receiving PCR results, and the shipping delay largely ensure that patients will not be treated early.

Extreme conflicts of interest. This trial has extreme conflicts of interest, being funded by an organization that chose not to recommend treatment while providing no quantitative analysis, no reference to the majority of the research, and no updates for new research for a very long period [ivmmeta.com]. Further, a majority of the panel providing the recommendation has major conflicts of interest [ivmmeta.com]. Also see [trialsitenews.com (D), trialsitenews.com (E)].

Treatment delay-response relationship. Subgroup results for treatment delays 13, 11, 9, 7, and 5 show monotonically improving results (less than 1% probability due to chance). ≤ 3 days may have very few patients, and is within confidence limits for monotonically improving results. Improved efficacy for earlier treatment matches extensive results for ivermectin and other COVID-19 treatments [c19early.com], however authors ignore this trend, claiming only a lack of statistical significance for one specific binary threshold (which may have few patients on one side), and authors have not initiated an early treatment trial.

Randomization failure. The placebo arm includes participants selected for other drugs, with drug specific exclusions. This breaks the randomization because the populations for each drug are different.

Blinding failure. The placebo arm included multiple regimens matching different treatment arms, hence some participants will know they are not in the ivermectin arm, and others will know that there is a higher probability of them being in the ivermectin arm than the placebo arm. This may be more important given the politicization in the study country. The fluticasone arm and matching placebo use an inhaler, the fluvoxamine arm uses 10 days treatment. Mached placebo analysis should be provided.

Disingenuous conclusion. The conclusion states that treatment did not lower mortality of hospitalization, however it is impossible to lower zero mortality. While authors do not indicate COVID-19 versus other hospitalization, statistically significant reduction in hospitalization would require at minimum 79%

efficacy, but for COVID-19 hospitalization it is likely impossible based on expected non-COVID-19 hospitalizations. The trial is underpowered by design due to selection of a low-risk population. Note that among the 90 severe cases, statistically significant efficacy is reported.

Up to 6 days shipping delay. The ≤ 7 days inclusion criterion and the 13 days subgroup suggests there was up to 6 days shipping delay (in part due to no weekend shipping). COVID-19 is an acute disease (which may or may not be mild). Participants cannot be expected to wait 1-2 days or longer for treatment. Chances are that patients feel better by the time medication arrives and do not take the medication, which may explain why adherence is not reported, or their condition became worse and they found alternative immediate care elsewhere.

IDMC not independent. The IDMC vice chair was reportedly on the NIH panel that did not recommend treatment despite strong evidence, and provided no quantitative analysis, no reference to the majority of the research, and no updates for new research for a very long period [ivmmeta.com].

No adherence data. Authors provide no adherence data. Non-adherence may de-power the trial and may harm randomization.

Low risk patients. Authors focus on patients at low risk of COVID-19 severe outcomes, which ensures an underpowered trial, with only one death which may not be due to COVID-19. All-cause mortality and hospitalization become less meaningful, with a significant contribution from non-COVID-19 causes.

Subject to participant fraud. The self-reported design, partial blinding, and absence of professional medical examination opens the trial to participant fraud, which may be significant due to extreme politicization in the study country.

Not enough tablets provided. Participants were supplied 15 7mg tablets and instructed to take the number of tablets to approximate 400 μ g/kg, however not enough tablets were provided for patients with higher weights, indicating that higher risk patients received lower dosage. 41% of patients had BMI > 30 and subgroups include BMI 50.

Over 2x greater severe dyspnea at baseline for ivermectin. There was over 2x greater severe dyspnea in the ivermectin arm at baseline (1.65% vs. 0.71%), which may be very important for analyzing mortality and hospitalization.

Authors suggest high-income country healthcare is better, however almost all patients received no active SOC. Authors suggest the operation in a high-income country with an associated healthcare system is a notable strength, however the study country provided no active treatment for almost all patients in the study, in contrast to many lower income countries that provide multiple treatments. Remdesivir, monoclonal antibodies, and paxlovid are very difficult to obtain and rarely used for outpatients in the study country. High income countries also may have significantly higher conflicts of interest.

Placebo unspecified. Authors do not specify placebo details, only that packaging was identical. If the tablets were not identical, this would be an additional reason for blinding failure.

No breakdown of severe outcomes. Notably, no details are provided for the hospitalization and mortality events, which may have been more likely among patients with extremely late treatment, or influenced by the higher baseline severity in the ivermectin arm. No severe outcome results are provided for (relatively) early treatment.

Monotherapy with no SOC for most patients. Authors perform monotherapy and the standard of care for most patients in the study country included no active treatments. Other treatments were very rare - remdesivir 0.3%, monoclonal antibodies 3%, and paxlovid 0.1%. However, extensive and growing research shows greater and synergistic benefits from polytherapy. Many studies use polytherapy and/or the standard of care includes multiple active treatments.

No subgroup counts for treatment delay. Notably, no subgroup counts are provided for treatment delay, while they are provided for baseline symptoms and vaccination status. The number of patients with symptoms ≤ 3 days may have been very small given the design of the trial.

Skeptical prior not justified. The skeptical prior, which reduces the observed efficacy in the post-hoc primary outcome, is not justified based on the studies to date. The skeptical prior was pre-specified. Authors may argue that the prior is justified because the trial was designed to avoid showing efficacy.

What can be done better? This long list of issues details the flaws prohibiting any negative conclusion about early treatment. In fact, the results are extremely positive given the conditions. Despite extreme and obvious measures used to avoid showing efficacy, efficacy was still found. Running a better trial is a simple matter of avoiding the issues above. How do you ensure early treatment with high-risk patients? One example would be pre-enrolling nursing home patients, providing treatment packages in advance, and instructing local medical staff to initiate randomization, treatment, and monitoring immediately on symptoms. This would likely be cheaper to run, and easily extended to also study prophylaxis.

For additional issues see [\[trialsitenews.com \(F\)\]](https://trialsitenews.com).

López-Medina et al.

An open letter, signed by >100 physicians, concluding this study is fatally flawed can be found at [\[jamaletter.com\]](https://jamaletter.com).

This is a phone survey based RCT with low risk patients, 200 ivermectin and 198 control, showing lower mortality, lower disease progression, lower treatment escalation, and faster resolution of symptoms with treatment, without reaching statistical significance. Authors find the results of this trial alone do not support the use of ivermectin. However the effects are all positive, especially for serious outcomes which are unable to reach statistical significance with the very small number of events in the low risk population.

RCTs have a fundamental bias against finding an effect for interventions that are widely available — patients that believe they need treatment are more likely to decline participation and take the intervention [\[Yeh\]](#), i.e., RCTs are more likely to enroll low-risk participants that do not need treatment to recover (this does not apply to the typical pharmaceutical trial of a new drug that is otherwise unavailable). This trial was run in a community where ivermectin was available OTC and very widely known and used.

With the low risk patient population, there is little room for improvement with an effective treatment - 59/57% (IVM/control) recovered within the first 2 days to either "no symptoms" or "not hospitalized and no limitation of activities"; 73/69% within 5 days. Less than 3% of all patients ever deteriorated.

The primary outcome was changed mid-trial, it was originally clinical deterioration, which is more meaningful, and shows greater benefit. The new outcome of resolution of symptoms includes "not hospitalized and no limitation of activities" as a negative outcome and is not very meaningful in terms of

assessing how much treatment reduces serious outcomes. Using this measure could completely invalidate results - for example a treatment that eliminates all COVID-19 symptoms but has a temporary minor adverse event could be seen as worse.

Authors state that "preliminary reports of other randomized trials of ivermectin as treatment for COVID-19 with positive results have not yet been published in peer-reviewed journals", however there were 8 peer-reviewed RCTs with positive effects published prior to this paper (and 19 total peer-reviewed studies with positive effects).

Authors advised taking ivermectin on an empty stomach, reducing lung tissue concentration by ~2.5x [Guzzo].

76 patients were excluded due to control patients receiving ivermectin. However, there was a similar percentage of adverse events like diarrhea, nausea, and abdominal pain in both treatment and control groups. These are potential non-serious side effects of treatment and suggest that it is possible that many more control patients received some kind of treatment.

Ivermectin was widely used in the population and available OTC at the time of the study. The study protocol only excluded patients with previous ivermectin use within 5 days, however other trials often monitor effects 10+ days after the last dose [osf.io (B)].

This study reportedly has an ethical issue whereby participants were told the study drug was "D11AX22" [trialsitenews.com (G)]. The editor-in-chief of JAMA initially offered to help with this issue, but later indicated that "JAMA does not review consent forms", however the lead author reportedly confirmed the issue [francesoir.fr, trialsitenews.com (H), trialsitenews.com (I)].

The study protocol specifically allows "the use of other treatments outside of clinical trials". The paper provides no information on what other treatments were used, but other treatments were commonly used at the time. Additionally, the control group did about 5x better than anticipated for deterioration, also suggesting that the control patients used some kind of treatment. Patients that enroll in such a study may be more likely to learn about and use other treatments, especially since they do not know if they are receiving the study medication.

The study protocol was amended 4 times. Amendments 2-4 are provided but amendment 1 is missing. Amendment 2 increased the inclusion criteria to within 7 days of onset, including more later stage patients and reducing the expected effectiveness. The trial protocol lists "the duration of supplemental oxygen" as an outcome but the results for this outcome are missing.

Grants and/or personal fees, including in some cases during the conduct of the study, were provided by Sanofi Pasteur, GlaxoSmithKline, Janssen, Merck, and Gilead. For more details see [trialsitenews.com (J)].

For other confounding issues see [osf.io (C)] and additional issues can be found in the comments of the article [jamanetwork.com (B)]. Re-analysis of the raw data has been reported to show a significant positive effect [twitter.com (AL)].

Vallejos et al.

With only 7% hospitalization, this trial is underpowered. The trial primarily includes low-risk patients that recover quickly without treatment, leaving minimal room for improvement with treatment. 74 patients had symptoms for ≥ 7 days and more than 25% of patients were hospitalized within 1 day (Figure S2).

Among the 7 patients requiring ventilation, authors note that the earlier requirement in the ivermectin group may be due to those patients having higher severity at baseline. However, authors know the answer to this - it is unclear why it is not reported. There were more adverse events in the placebo group than the ivermectin group, suggesting a possible issue with dispensing or non-trial medication usage.

The companion prophylaxis trial [\[IVERCOR PREP\]](#), which reported more positive results, has not yet been formally published, suggesting a negative publication bias.

Authors pre-specify multivariate analysis but do not present it, however multivariate analysis could significantly change the results. Consider for example if just a few extra patients in the ivermectin group were in severe condition based on baseline SpO2. The lower mean SpO2 in the ivermectin group, and the shorter time to ventilation, are consistent with this being the case. Additionally, there are 14% more male patients in the ivermectin group.

An extremely large percentage of patients (55%) were excluded based on ivermectin use in the last 7 days. However, ivermectin may retain efficacy much longer (for example antiparasitic activity may persist for months [\[Canga\]](#)). A significant number of patients may also misrepresent their prior and future usage – the population is clearly aware of ivermectin, and patients with progressing disease may be motivated to take it, knowing that they may be in the control group. Another report states that 12,000 patients were excluded for recent use of ivermectin [\[scidev.net\]](#).

RCTs have a fundamental bias against finding an effect for interventions that are widely available – patients that believe they need treatment are more likely to decline participation and take the intervention [\[Yeh\]](#), i.e., RCTs are more likely to enroll low-risk participants that do not need treatment to recover (this does not apply to the typical pharmaceutical trial of a new drug that is otherwise unavailable). This trial was run in a community where ivermectin was very widely known and used.

For other issues see [\[trialsitenews.com \(K\)\]](#).

Beltran Gonzalez et al.

Another study reports results on a larger group of patients in the same hospital, showing ivermectin mortality RR 0.81 [0.53-1.24] [\[Guzman\]](#).

Questions have been raised about this study and the early termination of the study and discontinuation of treatments, because the hospital statistics show a dramatically lower (~75%) case fatality rate during the period of the study [\[web.archive.org \(B\)\]](#) (data from [\[gob.mx\]](#)).

Date	Cases	Deaths	CFR
3/2020	2	1	50%
4/2020	4	1	25%
5/2020	13	1	8%
6/2020	37	2	5%
7/2020	65	5	8%
8/2020	79	23	29%
9/2020	54	12	22%

10/2020	62	21	34%
11/2020	80	26	33%
12/2020	41	13	32%

Several other inconsistencies have been reported [Chamie].

Although the data from this study is reported to be available and has been shared with an anti-treatment group, independent researchers have been unable to obtain the data for verification [Chamie, twitter.com (AM)].

Popp et al.

This meta analysis is designed to exclude most studies. Authors select a small subset of studies, with a majority of results based on only 1 or 2 studies. Authors split up studies which dilutes the effects and results in a lack of statistical significance for most outcomes. Authors perform 16+ meta analyses with very few studies in each analysis, and do not combine the evidence from all studies. However, we can consider the probability of the observed results across all outcomes.

Authors find positive results for 11 of 12 primary efficacy outcomes with events, or 16 of 18 including secondary outcomes. One of the primary outcomes and two of the secondary outcomes show statistically significant improvements in isolation. If we assume independence, the probability that 11+ of 12 primary efficacy outcomes were positive for an ineffective treatment is $p = 0.003$. For 16+ of 18 outcomes we get $p = 0.0007$. This simple analysis does not take into account the magnitude of positive effects, or the dependence due to some studies contributing multiple outcomes, however observation suggests that a full analysis of the combined evidence is likely to show efficacy.

The study is entirely retrospective in the current version. The protocol is dated April 20, 2021, and the most recent study included is from March 9, 2021. The protocol was modified after publication in order to include a close to null result ([Beltran Gonzalez] "patients discharged without respiratory deterioration or death at 28 days"), so the current protocol is dated July 28, 2021.

Authors excluded many studies by requiring results at a specific time, for example mortality, ventilation, etc. required results at exactly 28 days. Authors excluded all prophylaxis studies by requiring results at exactly 14 days.

Studies comparing with other medications were excluded, however these studies confirm efficacy of ivermectin. The only case where they could overstate the efficacy of ivermectin is if the other medication was harmful. There is some evidence of this for excessive dosage/very late stage use, however that does not apply to any of the studies here.

Studies using combined treatment were excluded, even when it is known that the other components have minimal or no effect. 3 of 4 RCTs with combined treatment use doxycycline in addition [Butler]. Other studies were excluded by requiring PCR confirmation.

Authors are inconsistent regarding active comparators. They state that hydroxychloroquine "does not work", yet excluded trials comparing ivermectin to a drug they hold to be inactive. On the other hand, remdesivir was an acceptable comparator, although it is considered to be effective standard of care in some locations [Fordham].

Authors fail to recognize that Risk of Bias (RoB) domains such as blinding are far less important for the objective outcome of mortality.

Authors include **[Beltran Gonzalez]** as "moderate" COVID-19, however patients in this study were in severe condition (baseline SatO2 83).

[Fordham] summarizes several problems:

- unsupported assertions of adverse reactions to ivermectin, and the outdated claim that unsafe dosing would be needed to be effective;
- a demand for PCR or antigen testing, without analysis of reliability and not universally available even in developed countries at the start of the pandemic;
- contradictions in the exclusion criteria, including placebo and approved SoC comparators, but rejecting hydroxychloroquine, though held to be ineffective (and an approved SoC in some jurisdictions);
- inclusion of "deemed active" comparators whilst excluding "potentially active" ones;
- exclusion of combination therapies, though the norm among practising clinicians;
- the rejection of other than RCTs when the objective is a "complete evidence profile";
- arbitrary time-points for outcome measures, excluding non-compliant trials;
- fragmentation of data by location of care under varying hospitalisation criteria;
- the resulting focus on a small fraction of the available clinical evidence, with most comparisons based on single studies with no meta-analysis possible;
- a resulting inpatient mortality comparison with fewer patients than a June 2020 confounder-matched study;
- no conclusion on the headline mortality outcome, when multiple lines of evidence from elsewhere (including the WHO) point to significant mortality advantage.

Cochrane was reputable in the past, but is now controlled by pharmaceutical interests. For example, see the news related to the expulsion of founder Dr. Gøtzsche and the associated mass resignation of board members in protest **[blogs.bmj.com, bmj.com, en.x-mol.com]**. For another example of bias see **[ebm.bmj.com]**.

The BiRD group gave the following early comment: "Yesterday's Cochrane review surprisingly doesn't take a pragmatic approach comparing ivermectin versus no ivermectin, like in the majority of other existing reviews. It uses a granular approach similar to WHO's and the flawed Roman et al paper, splitting studies up and thereby diluting effects. Consequently, the uncertain conclusions add nothing to the evidence base. A further obfuscation of the evidence on ivermectin and an example of research waste. Funding conflicts of interests of the authors and of the journal concerned should be examined."

Roman et al.

This is a severely flawed meta analysis. An open letter signed by 40 physicians detailing errors and flaws, and requesting retraction, can be found at **[trialsitenews.com (L)]**. See also **[bird-group.org]**.

Authors cherry-pick to include only 4 studies reporting non-zero mortality and they initially claimed a mortality RR of 1.11 [0.16-7.65]. However, they reported incorrect values for Niaee et al., claiming an RR of 6.51 [2.18-19.45], when the correct RR for Niaee et al. is 0.18 [0.06-0.55]. After correction, their cherry-

picked studies show >60% mortality reduction, however authors did not correct the conclusion.

Similarly, for viral clearance and NCT04392713, they report 20/41 treatment, 18/45 control, whereas the correct day 7 clearance numbers are 37/41 and 20/45 (sum of clearance @72hrs and @7 days), or 17/41 and 2/45 @72 hrs.

The duration of hospital stay for Niaee et al. is also incorrectly reported, showing a lower duration for the control group.

All of the errors are in one direction - incorrectly reporting lower than actual efficacy for ivermectin. Authors claim to include all RCTs excluding prophylaxis, however they only include 10 of the 24 non-prophylaxis RCTs (28 including prophylaxis at the time of publication). Authors actually reference meta analyses that do include the missing RCTs, so they should be aware of the missing RCTs.

The PubMed search strategy provided is syntactically incorrect. For additional errors, see [\[pubpeer.com\]](https://pubpeer.com). Also see [\[roundingtheearth.substack.com\]](https://roundingtheearth.substack.com).

The authors state that they have no conflicts of interest on medRxiv, however Dr. Pasupuleti's affiliation is Cello Health, whose website [\[cellohealth.com\]](https://cellohealth.com) notes that they provide services such as "brand and portfolio commercial strategy for biotech and pharma", and that their clients are "24 of the top 25 pharmaceutical companies".

Revisions

Please submit updates and corrections at <https://ivmmeta.com/>.

6/24: We added [\[Mirahmadizadeh\]](#).

6/16: We updated the [ACTIV-6](#) analysis.

6/16: We added [\[Rezai, Rezai \(B\)\]](#).

6/12: We added [\[Naggie\]](#).

6/1: We updated the [Together Trial](#) analysis.

5/30: We added [\[George\]](#).

5/30: We updated the [Together Trial](#) analysis.

5/27: We added [\[Rocha\]](#).

4/25: [SSC discussion](#) updates.

4/17: We added a section on preclinical research.

4/16: We added discussion of the [NIH recommendation](#).

4/9: We updated the [Together Trial](#) analysis.

4/8: We added [\[Ravikirti\]](#).

4/5: We added preprint discussion based on **[Zeraatkar]**, and updated the Together Trial analysis.

4/2: We updated the Together Trial analysis.

3/30: We updated **[Reis]** to the journal version.

3/21: Strongyloides discussion updates.

3/3: We updated **[Beltran Gonzalez]** to the journal version.

3/2: We added **[Soto]**.

2/28: We added **[Efimenko]**.

2/25: We added **[Thairu]**.

2/23: We updated **[Mayer]** to the journal version.

2/18: We updated **[Lim]** to the journal version.

2/2: We added **[Manomaipiboon]**.

1/28: We added **[de Jesús Ascencio-Montiel]**.

1/21: We added **[Zubair]**.

1/17: We added an explanation of why funnel plot analysis is not valid in this case.

1/16: We added RCT viral clearance analysis and corrected missing symptomatic case results in the case analysis.

1/15: We updated **[Kerr]** to the journal version.

1/15: We corrected hospitalization group sizes in **[Buonfrate]**.

1/13: We added **[Abbas, Baguma]**.

1/11: We updated **[Kerr]** to the latest results, and added discussion of **[Beltran Gonzalez]**.

1/7: We updated **[Buonfrate]** to the journal version, and we updated **[Kerr]** to the latest results.

12/31: We added **[Shimizu]**.

12/29: We added **[Mustafa]**.

12/26: We updated **[Kerr]** to the revised version of the paper.

12/16: We added **[Jamir]**.

12/11: We added **[Kerr]**.

12/8: We added analysis of the number of independent research groups reporting statistically significant positive results.

12/5: We added [\[Ferreira\]](#).

12/5: We added [\[Rezk\]](#).

12/3: A note on Bernigaud: continuity correction uses the reciprocal of the contrasting arm [\[Sweeting\]](#), as detailed in the appendix. We previously limited the size of the control group when showing the total number of patients, however this was confusing for people that did not read the details, as discussed below. The full group size has always been used when computing the RR.

12/1: [Strongyloides](#) discussion updates.

11/30: We corrected [\[Ghuri\]](#) to use the event counts.

11/24: We added [\[Ozer\]](#).

11/24: [SSC](#) discussion updates.

11/21: [Strongyloides](#) discussion updates.

11/20: [Strongyloides](#) discussion updates.

11/19: We added analysis by [strongyloides prevalence](#), and updated it to match the revised classification used in the comparable analysis.

11/19: We added additional exclusion analyses in the [supplementary data](#).

11/18: We incorrectly included [\[López-Medina\]](#) as a study not reporting use of steroids, however they report 6% usage in the control group.

11/18: We added [\[Samajdar\]](#).

11/17: [SSC](#) response.

11/16: Discussion updates.

11/12: We now show the number of studies reporting statistically significant results for any outcome, primary outcomes, and the most serious outcome.

11/9: Discussion updates.

11/5: We added discussion of strongyloides, comparison with the recent [molnupiravir](#) approval, and notes on [recruitment for remote outpatient delayed treatment trials](#).

11/3: We added [\[Lim\]](#).

11/3: Discussion updates.

10/29: Discussion updates including [GMK vitamin D](#) analysis.

10/28: Discussion updates.

10/26: We updated the [GMK](#) response.

10/24: We added additional exclusion analyses for individual outcomes.

10/21: We added **[Borody]**.

10/19: Discussion updates.

10/18: **[Ghuri]** was updated to the journal version.

10/16: We added a summary plot for all results.

10/13: We added primary outcome analysis and additional exclusion analyses. Niaee et al. has been reported as pending retraction and has been removed. 10/27 update: the journal has reported that this is incorrect — no retraction is pending.

10/11: Discussion updates. Niaee et al. exclusion. Updates to the [study notes](#) including discussion of [Vallejos et al.](#) and additional issues in the [Together Trial](#). Discussion of [inherent bias in RCTs for widely available interventions](#).

10/8: Discussion updates.

10/7: Samaha et al. has been reported as pending retraction and has been removed. There was no significant change in the results.

10/4: Merck discussion updates.

9/29: We corrected a display error causing a few points to be missing in Figure 4.

9/27: We added **[Mayer]**.

9/24: We added a graph of variants over time for the [Together Trial discussion](#) and corrected outcome discussion for Popp et al.

9/22: Discussion updates.

9/20: Discussion updates.

9/18: We added **[Buonfrate]**, and updated discussion of the [Together Trial](#).

9/17: We added study notes.

9/15: Discussion updates.

9/14: FDA discussion updates.

9/9: We added sensitivity analysis to compute the minimum number of studies that need to be excluded in order to avoid showing efficacy. Discussion updates.

9/7: Discussion updates.

9/6: We corrected **[Espitia-Hernandez]** to use the reported recovery time and added missing recovery and viral clearance results.

9/3: We updated discussion and excluded Carvallo et al. in the exclusion analysis.

8/27: We updated **[Morgenstern (B)]** with the journal version of the article.

8/26: We updated **[Mohan]** with the journal version of the article.

8/16: We updated **[Reis]** with event counts.

8/15: We updated discussion and made the abstract more concise.

8/12: We added **[Elavarasi, Reis]**.

8/8: We updated discussion in the responses.

8/6: We updated **[Behera (B)]** with the journal version of the article.

8/5: We added **[Mondal]**.

8/4: We added discussion of the FDA recommendation.

8/3: We added discussion in the responses section.

8/2: We added analysis restricted to serious outcomes and analysis restricted to recovery, and we added discussion in the responses section.

7/31: We added discussion in the responses section related to *in vitro* evidence and therapeutic concentrations.

7/29: We added discussion in the responses section.

7/20: We updated **[Hashim]** with the journal version of the article.

7/16: We updated **[Ravikirti (B)]** with the journal version of the article.

7/15: Elgazzar et al. was withdrawn by the preprint server and has been removed.

7/9: We added **[Hazan]**.

7/8: We updated **[Cadegiani]** to the journal version.

7/6: We previously limited the size of the control group for **[Bernigaud]** when calculating the total number of patients, however this was confusing for many people that did not read the details. We now show the original counts and note the larger size of the control group in the text.

7/3: We added **[Vallejos]**.

7/2: We updated Niaee et al. to the journal version.

6/21: We added more information to the abstract.

6/19: We updated **[Bryant]** to the journal version.

6/19: **[Beltran Gonzalez]** was incorrectly included in the peer-reviewed analysis.

6/18: We added **[Krolewiecki]**.

6/15: We added **[Aref]**.

6/7: We added *[Hariyanto]*.

6/5: We added *[Ahsan]*.

6/2: We added *[Abd-El salam]*.

5/31: *[Biber]* was updated to the preprint.

5/26: Samaha et al. was updated to the journal version.

5/18: We added analysis of Merck's recommendation.

5/17: We added *[Szente Fonseca]*.

5/15: We updated the discussion of the WHO analysis.

5/13: We updated *[Mahmud]* to the journal version.

5/10: We added *[Faisal]*.

5/10: We added additional information in the abstract.

5/8: We added *[Merino]*.

5/7: We updated *[Shahbaznejad]* to the journal version, which includes additional outcomes not reported earlier.

5/6: We updated *[Chahla]* to the Research Square preprint.

5/6: We added a comparison of CDC recommendations.

5/6: We added mechanical ventilation and ICU admission analysis.

5/6: We updated discussion based on peer review including discussion of heterogeneity, exclusion based sensitivity analysis, and search criteria.

5/5: We updated *[Okumus]* to the journal paper.

5/5: We previously limited the size of the control group in *[Bernigaud]* to be the same as the treatment group for calculation of the total number of patients. This is now also reflected and noted in the forest plots.

5/4: We added *[Loue]*.

4/30: We added analysis of the WHO meta analysis and updated *[Kory]* to the journal version.

4/28: We added the WHO meta analysis results for comparison.

4/27: We added analysis restricted to hospitalization results and a comparison with the evidence base used in the approval of other COVID-19 treatments.

4/26: We added notes on heterogeneity.

4/25: We updated **[Biber]** to the latest results reported at the International Ivermectin for Covid Conference.

4/18: We updated **[Morgenstern]** to the preprint.

4/16: We added **[Morgenstern]**.

4/14: We added **[Seet]**.

4/10: We added **[Kishoria]**.

4/9: We corrected a duplicate entry for **[Bukhari]**.

4/7: We identified studies where minimal detail is currently available in the forest plots.

4/5: We added **[Mourya]**.

4/4: We added event counts to the forest plots.

3/31: We updated **[Chahla (B)]** to the preprint.

3/30: We added **[Chahla]**.

3/28: We highlighted and added discussion for studies that use combined treatments.

3/26: We added **[Tanioka]**.

3/25: We added **[Huvmek]**.

3/17: We added **[Nardelli]**.

3/12: We added **[Bryant, Roy]**.

3/10: We added **[Pott-Junior]**.

3/6: We added **[Chowdhury]** and we identify studies that compare with another treatment.

3/5: We added discussion of pooled effects (we show both pooled effects and individual outcome results).

3/4: We added **[López-Medina]**, and we added more information in the abstract.

3/3: We updated the graphs to indicate the time period for the dosage column, now showing the dosage over one month for prophylaxis and over four days for other studies.

3/2: We updated **[IVERCOR PREP]** with the latest results **[Vallejos (B)]**.

2/27: We added analysis restricted to peer reviewed studies.

2/24: We added a comparison of the evidence base and WHO approval status for the use of ivermectin with scabies and COVID-19. We updated **[Okumuş]** with the Research Square preprint.

2/23: We added **[Beltran Gonzalez]**.

2/18: We updated **[Babalola]** to the journal version of the paper.

2/17: We added **[Elalfy]**, and we added analysis restricted to viral clearance outcomes, and mortality results restricted to RCTs.

2/16: We updated **[Behera]** to the journal version of the paper.

2/15: We added **[Behera (B)]**.

2/14: We added analysis restricted to COVID-19 case outcomes, and we added additional results in the abstract.

2/12: We added **[Biber]**.

2/11: We added more details on the analysis of prospective vs. retrospective studies.

2/10: We added **[Lima-Morales]**.

2/5: We updated **[Bukhari]** to the preprint.

2/2: We added **[Mohan]**.

1/26: We updated **[Shouman]** with the journal version of the article.

1/25: We updated **[IVERCOR PREP]** with the recently released results.

1/19: We added **[Shahbaznejad]** and Samaha et al. **[Chaccour (B)]** was updated to the journal version of the paper.

1/17: We added **[Bukhari]**.

1/16: We moved the analysis with exclusions to the main text, and added additional commentary.

1/15: We added the effect measured for each study in the forest plots.

1/12: We added **[Okumuş]**.

1/11: We added **[Chahla (B)]**.

1/10: We put all prophylaxis studies in a single group.

1/9: We added **[Ravikirti (B)]**. Due to the much larger size of the control group in **[Bernigaud]**, we limited the size of the control group to be the same as the treatment group for calculation of the total number of patients.

1/7: We added direct links to the study details in the chronological plots.

1/6: We added **[Babalola]**.

1/5: We added direct links to the study details in the forest plots.

1/2/2021: We added dosage information and we added the number of patients to the forest plots.

12/31: We added additional details about the studies in the appendix.

12/29: We added meta analysis excluding late treatment.

12/27: We added the total number of authors and patients.

12/26: We added [Carvalho (B), IVERCOR PREP].

12/17: We added [Alam].

12/16: We added [Ghauri].

12/11: We added [Soto-Becerra].

12/7: We added [Chaccour (B)].

12/2: We added [Ahmed].

11/26/2020: Initial revision.

Appendix 1. Methods and Data

We performed ongoing searches of PubMed, medRxiv, ClinicalTrials.gov, The Cochrane Library, Google Scholar, Collabovid, Research Square, ScienceDirect, Oxford University Press, the reference lists of other studies and meta-analyses, and submissions to the site c19ivermectin.com, which regularly receives submissions of studies upon publication. Search terms were ivermectin and COVID-19 or SARS-CoV-2, or simply ivermectin. Automated searches are performed every hour with notification of new matches. The broad search terms result in a large volume of new studies on a daily basis which are reviewed for inclusion. All studies regarding the use of ivermectin for COVID-19 that report a comparison with a control group are included in the main analysis. Sensitivity analysis is performed, excluding studies with major issues, epidemiological studies, and studies with minimal available information. This is a living analysis and is updated regularly.

We extracted effect sizes and associated data from all studies. If studies report multiple kinds of effects then the most serious outcome is used in pooled analysis, while other outcomes are included in the outcome specific analyses. For example, if effects for mortality and cases are both reported, the effect for mortality is used, this may be different to the effect that a study focused on. If symptomatic results are reported at multiple times, we used the latest time, for example if mortality results are provided at 14 days and 28 days, the results at 28 days are used. Mortality alone is preferred over combined outcomes. Outcomes with zero events in both arms were not used (the next most serious outcome is used – no studies were excluded). For example, in low-risk populations with no mortality, a reduction in mortality with treatment is not possible, however a reduction in hospitalization, for example, is still valuable. Clinical outcome is considered more important than PCR testing status. When basically all patients recover in both treatment and control groups, preference for viral clearance and recovery is given to results mid-recovery where available (after most or all patients have recovered there is no room for an effective treatment to do better). If only individual symptom data is available, the most serious symptom has priority, for example difficulty breathing or low SpO₂ is more important than cough. When results provide an odds ratio, we computed the relative risk when possible, or converted to a relative risk according to [Zhang]. Reported confidence intervals and *p*-values were used when available, using adjusted values when provided. If multiple types of adjustments are reported including propensity score matching (PSM), the PSM results are used. Adjusted primary outcome results have preference over unadjusted results for a more serious outcome when the adjustments significantly alter results. When

needed, conversion between reported p -values and confidence intervals followed [Altman, Altman (B)], and Fisher's exact test was used to calculate p -values for event data. If continuity correction for zero values is required, we use the reciprocal of the opposite arm with the sum of the correction factors equal to 1 [Sweeting]. Results are expressed with $RR < 1.0$ favoring treatment, and using the risk of a negative outcome when applicable (for example, the risk of death rather than the risk of survival). If studies only report relative continuous values such as relative times, the ratio of the time for the treatment group versus the time for the control group is used. Calculations are done in Python (3.9.13) with scipy (1.8.0), pythonmeta (1.26), numpy (1.22.2), statsmodels (0.14.0), and plotly (5.6.0).

Forest plots are computed using PythonMeta [Deng] with the DerSimonian and Laird random effects model (the fixed effect assumption is not plausible in this case) and inverse variance weighting. Mixed-effects meta-regression results are computed with R (4.1.2) using the metafor (3.0-2) and rms (6.2-0) packages, and using the most serious sufficiently powered outcome. Forest plots show simplified dosages for comparison, these are the total dose in the first four days for treatment, and the monthly dose for prophylaxis, for a 70kg person. For full dosage details see below.

We received no funding, this research is done in our spare time. We have no affiliations with any pharmaceutical companies or political parties.

We have classified studies as early treatment if most patients are not already at a severe stage at the time of treatment (for example based on oxygen status or lung involvement), and treatment started within 5 days of the onset of symptoms. If studies contain a mix of early treatment and late treatment patients, we consider the treatment time of patients contributing most to the events (for example, consider a study where most patients are treated early but late treatment patients are included, and all mortality events were observed with late treatment patients). We note that a shorter time may be preferable. Antivirals are typically only considered effective when used within a shorter timeframe, for example 0-36 or 0-48 hours for oseltamivir, with longer delays not being effective [McLean, Treanor].

Note that the size of the control group in [Bernigaud] is significantly larger than the treatment group. We previously limited the size to be the same as that of the treatment group for calculation of the number of patients, however this was confusing to many people that did not read the details.

A summary of study results is below. Please submit updates and corrections at <https://ivmmeta.com/>.

Early treatment.

Effect extraction follows pre-specified rules as detailed above and gives priority to more serious outcomes. Only the first (most serious) outcome is used in pooled analysis, which may differ from the effect a paper focuses on. Other outcomes are used in outcome specific analyses.

[Abbas] , 12/31/2021, Double Blind Randomized Controlled Trial, placebo-controlled, China, Asia, peer-reviewed, 3 authors, dosage 300µg/kg days 1-5, excluded in exclusion analyses: very minimal patient information, three different results for the recovery outcome, selective omission of the statistically significant recovery p -value, and other inconsistencies.	risk of death, 4.0% higher, $RR\ 1.04$, $p = 1.00$, treatment 1 of 99 (1.0%), control 1 of 103 (1.0%).
	deterioration of 2 or more points, 40.5% lower, $RR\ 0.59$, $p = 0.54$, treatment 4 of 99 (4.0%), control 7 of 103 (6.8%), $NNT\ 36$.
	escalation of care, 14.9% lower, $RR\ 0.85$, $p = 0.82$, treatment 9 of 99 (9.1%), control 11 of 103 (10.7%), $NNT\ 63$.

	fever during study, 17.9% lower, RR 0.82, $p = 0.58$, treatment 15 of 99 (15.2%), control 19 of 103 (18.4%), NNT 30.
	risk of no recovery, 35.6% lower, RR 0.64, $p = 0.04$, treatment 26 of 99 (26.3%), control 42 of 103 (40.8%), NNT 6.9, primary outcome.
	recovery time, 30.8% lower, relative time 0.69, $p = 0.08$, treatment 99, control 103, primary outcome.
<p>[Ahmed], 12/2/2020, Double Blind Randomized Controlled Trial, Bangladesh, South Asia, peer-reviewed, mean age 42.0, 15 authors, average treatment delay 3.83 days, dosage 12mg days 1-5, the ivermectin + doxycycline group took only a single dose of ivermectin.</p>	<p>risk of unresolved symptoms, 85.0% lower, RR 0.15, $p = 0.09$, treatment 0 of 17 (0.0%), control 3 of 19 (15.8%), NNT 6.3, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 7, fever, ivermectin (5 days), primary outcome.</p>
	risk of unresolved symptoms, 62.7% lower, RR 0.37, $p = 0.35$, treatment 1 of 17 (5.9%), control 3 of 19 (15.8%), NNT 10, day 7, fever, ivermectin (1 day) + doxycycline.
	risk of no viral clearance, 75.6% lower, HR 0.24, $p = 0.03$, treatment 11 of 22 (50.0%), control 20 of 23 (87.0%), NNT 2.7, adjusted per study, day 7, ivermectin (5 days).
	risk of no viral clearance, 56.5% lower, HR 0.43, $p = 0.22$, treatment 16 of 23 (69.6%), control 20 of 23 (87.0%), NNT 5.8, adjusted per study, day 7, ivermectin (1 day) + doxycycline.
	risk of no viral clearance, 63.0% lower, HR 0.37, $p = 0.02$, treatment 5 of 22 (22.7%), control 14 of 23 (60.9%), NNT 2.6, adjusted per study, day 14, ivermectin (5 days).
	risk of no viral clearance, 41.2% lower, HR 0.59, $p = 0.19$, treatment 9 of 23 (39.1%), control 14 of 23 (60.9%), NNT 4.6, adjusted per study, day 14, ivermectin (1 day) + doxycycline.
	time to viral-, 23.6% lower, relative time 0.76, $p = 0.02$, treatment 22, control 23, ivermectin (5 days).
	time to viral-, 9.4% lower, relative time 0.91, $p = 0.27$, treatment 23, control 23, ivermectin (1 day) + doxycycline.

<p>[Aref], 6/15/2021, Randomized Controlled Trial, Egypt, Africa, peer-reviewed, 7 authors, dosage not specified, trial NCT04716569.</p>	<p>relative duration of fever, 63.2% lower, relative time 0.37, $p < 0.001$, treatment 57, control 57, primary outcome.</p>
	<p>relative duration of dyspnea, 56.4% lower, relative time 0.44, $p < 0.001$, treatment 57, control 57.</p>
	<p>relative duration of anosmia, 68.8% lower, relative time 0.31, $p < 0.001$, treatment 57, control 57.</p>
	<p>relative duration of cough, 64.3% lower, relative time 0.36, $p < 0.001$, treatment 57, control 57.</p>
	<p>risk of no viral clearance, 78.6% lower, RR 0.21, $p = 0.004$, treatment 3 of 57 (5.3%), control 14 of 57 (24.6%), NNT 5.2.</p>
	<p>time to viral-, 35.7% lower, relative time 0.64, $p < 0.001$, treatment 57, control 57.</p>
<p>[Babalola], 1/6/2021, Double Blind Randomized Controlled Trial, Nigeria, Africa, peer-reviewed, baseline oxygen required 8.3%, 10 authors, dosage 12mg or 6mg q84h for two weeks, this trial compares with another treatment - results may be better when compared to placebo.</p>	<p>adjusted risk of viral+ at day 5, 63.9% lower, RR 0.36, $p = 0.11$, treatment 40, control 20, adjusted per study.</p>
	<p>relative ΔSpO_2 (unadjusted), 41.5% better, RR 0.59, $p = 0.07$, treatment 38, control 18, figure 3.</p>
	<p>risk of no viral clearance, 58.0% lower, HR 0.42, $p = 0.01$, treatment 20, control 20, 12mg - Cox proportional hazard model.</p>
	<p>risk of no viral clearance, 40.5% lower, HR 0.60, $p = 0.12$, treatment 20, control 20, 6mg - Cox proportional hazard model.</p>
	<p>time to viral-, 49.2% lower, relative time 0.51, $p = 0.02$, treatment 20, control 20, 12mg, primary outcome.</p>
	<p>time to viral-, 34.4% lower, relative time 0.66, $p = 0.08$, treatment 20, control 20, 6mg.</p>
<p>[Biber], 2/12/2021, Double Blind Randomized Controlled Trial, Israel, Middle East, preprint, 10 authors, average treatment delay 4.0 days, dosage 12mg days 1-3, 15mg for patients $\geq 70\text{kg}$, trial NCT04429711.</p>	<p>risk of hospitalization, 70.2% lower, RR 0.30, $p = 0.34$, treatment 1 of 47 (2.1%), control 3 of 42 (7.1%), NNT 20.</p>
	<p>risk of no viral clearance, 44.8% lower, RR 0.55, $p = 0.04$, treatment 13 of 47 (27.7%), control 21 of 42 (50.0%), NNT 4.5, adjusted per study, odds ratio</p>

	converted to relative risk, multivariable logistic regression, day 6, Ct>30, primary outcome.
	risk of no viral clearance, 70.2% lower, RR 0.30, $p = 0.14$, treatment 2 of 47 (4.3%), control 6 of 42 (14.3%), NNT 10.0, day 10, non-infectious samples (Ct>30 or non-viable culture).
	risk of no viral clearance, 82.1% lower, RR 0.18, $p = 0.01$, treatment 2 of 47 (4.3%), control 10 of 42 (23.8%), NNT 5.1, day 8, non-infectious samples (Ct>30 or non-viable culture).
	risk of no viral clearance, 75.6% lower, RR 0.24, $p = 0.02$, treatment 3 of 47 (6.4%), control 11 of 42 (26.2%), NNT 5.0, day 6, non-infectious samples (Ct>30 or non-viable culture).
	risk of no viral clearance, 65.1% lower, RR 0.35, $p = 0.05$, treatment 4 of 28 (14.3%), control 9 of 22 (40.9%), NNT 3.8, day 4, non-infectious samples (Ct>30 or non-viable culture).
	risk of no viral clearance, 51.9% lower, RR 0.48, $p = 0.08$, treatment 7 of 47 (14.9%), control 13 of 42 (31.0%), NNT 6.2, day 10, Ct>30.
	risk of no viral clearance, 57.9% lower, RR 0.42, $p = 0.02$, treatment 8 of 47 (17.0%), control 17 of 42 (40.5%), NNT 4.3, day 8, Ct>30.
	risk of no viral clearance, 44.7% lower, RR 0.55, $p = 0.049$, treatment 13 of 47 (27.7%), control 21 of 42 (50.0%), NNT 4.5, day 6, Ct>30.
	risk of no viral clearance, 31.9% lower, RR 0.68, $p = 0.16$, treatment 13 of 28 (46.4%), control 15 of 22 (68.2%), NNT 4.6, day 4, Ct>30.
<p>[Borody], 10/19/2021, retrospective, Australia, Oceania, preprint, 2 authors, study period 1 June, 2021 - 30 September, 2021, dosage 24mg days 1-10, this trial uses multiple treatments in the treatment arm (combined with zinc and doxycycline) - results of individual treatments may vary, excluded in exclusion analyses: preliminary report with minimal details.</p>	<p>risk of death, 92.3% lower, RR 0.08, $p = 0.03$, treatment 0 of 600 (0.0%), control 6 of 600 (1.0%), NNT 100, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).</p>
	<p>risk of hospitalization, 92.9% lower, RR 0.07, $p < 0.001$, treatment 5 of 600 (0.8%), control 70 of 600 (11.7%), NNT 9.2, primary outcome.</p>

<p>[Bukhari], 1/16/2021, Randomized Controlled Trial, Pakistan, South Asia, preprint, 10 authors, dosage 12mg single dose, trial NCT04392713.</p>	<p>risk of no viral clearance, 82.4% lower, RR 0.18, $p < 0.001$, treatment 4 of 41 (9.8%), control 25 of 45 (55.6%), NNT 2.2, day 7, primary outcome.</p>
	<p>risk of no viral clearance, 38.7% lower, RR 0.61, $p < 0.001$, treatment 24 of 41 (58.5%), control 43 of 45 (95.6%), NNT 2.7, day 3.</p>
<p>[Buonfrate], 9/6/2021, Double Blind Randomized Controlled Trial, Italy, Europe, peer-reviewed, 18 authors, average treatment delay 4.0 days, dosage 1200µg/kg days 1-5, arm B 600µg/kg, arm C 1200µg/kg, trial NCT04438850, excluded in exclusion analyses: significant unadjusted group differences, with 3 times as many patients in the ivermectin arms having the baseline visit in a hospital setting, and arm C having large differences in baseline gender, weight, cough, pyrexia, and anosmia, excessive dose for arm C.</p>	<p>risk of hospitalization, 210.7% higher, RR 3.11, $p = 0.47$, treatment 1 of 28 (3.6%), control 0 of 31 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm), arm B.</p>
	<p>risk of hospitalization, 610.0% higher, RR 7.10, $p = 0.11$, treatment 3 of 30 (10.0%), control 0 of 31 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm), arm C, very high dose, poorly tolerated with low compliance.</p>
	<p>relative change in viral load, RR 0.80, $p = 0.59$, treatment mean 2.5 (± 2.2) n=28, control mean 2.0 (± 4.4) n=29, day 7, arm B, primary outcome.</p>
	<p>relative change in viral load, RR 0.69, $p = 0.07$, treatment mean 2.9 (± 1.6) n=30, control mean 2.0 (± 2.1) n=29, day 7, arm C, primary outcome.</p>
<p>[Cadegiani], 11/4/2020, prospective, Brazil, South America, peer-reviewed, 4 authors, average treatment delay 2.9 days, dosage 200µg/kg days 1-3, this trial uses multiple treatments in the treatment arm (combined with AZ, nitazoxanide (82), HCQ (22), spironolactone (66), dutasteride (4)) - results of individual treatments may vary, excluded in exclusion analyses: control group retrospectively obtained from untreated patients in the same population.</p>	<p>risk of death, 78.3% lower, RR 0.22, $p = 0.50$, treatment 0 of 110 (0.0%), control 2 of 137 (1.5%), NNT 68, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), control group 1.</p>
	<p>risk of mechanical ventilation, 94.2% lower, RR 0.06, $p = 0.005$, treatment 0 of 110 (0.0%), control 9 of 137 (6.6%), NNT 15, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), control group 1.</p>
	<p>risk of hospitalization, 98.0% lower, RR 0.02, $p < 0.001$, treatment 0 of 110 (0.0%), control 27 of 137 (19.7%), NNT 5.1, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), control group 1.</p>
<p>[Carvalho (C)], 9/15/2020, prospective, Argentina, South America, peer-reviewed, mean age 55.7, 3 authors, dosage 36mg days 1, 8, dose varied depending on patient</p>	<p>risk of death, 85.4% lower, RR 0.15, $p = 0.08$, treatment 1 of 32 (3.1%), control 3 of 14 (21.4%), NNT 5.5, moderate/severe patients, the only treatment</p>

condition - mild 24mg, moderate 36mg, severe 48mg, this trial uses multiple treatments in the treatment arm (combined with dexamethasone, enoxaparin, and aspirin) - results of individual treatments may vary, excluded in exclusion analyses: minimal details of groups provided.	death was a patient already in the ICU before treatment, primary outcome.
[Chaccour (B)], 12/7/2020, Double Blind Randomized Controlled Trial, Spain, Europe, peer-reviewed, 23 authors, average treatment delay 1.0 days, dosage 400µg/kg single dose, trial NCT04390022.	risk of symptoms, 96.0% lower, OR 0.04, $p < 0.05$, treatment 12, control 12, logistic regression, chance of presenting any symptom, RR approximated with OR.
	viral load, 94.6% lower, relative load 0.05, $p < 0.01$, treatment 12, control 12, day 7 mid-recovery, average of gene E and gene N, data in supplementary appendix.
	risk of no viral clearance, 8.0% lower, RR 0.92, $p = 1.00$, treatment 12, control 12, primary outcome.
[Chahla], 3/30/2021, Cluster Randomized Controlled Trial, Argentina, South America, preprint, 9 authors, dosage 24mg days 1, 8, 15, 22, trial NCT04784481.	risk of no discharge, 86.9% lower, RR 0.13, $p = 0.004$, treatment 2 of 110 (1.8%), control 20 of 144 (13.9%), NNT 8.3, adjusted per study, odds ratio converted to relative risk, logistic regression, primary outcome.
[Chowdhury], 7/14/2020, Randomized Controlled Trial, Bangladesh, South Asia, peer-reviewed, 6 authors, dosage 200µg/kg single dose, this trial compares with another treatment - results may be better when compared to placebo, this trial uses multiple treatments in the treatment arm (combined with doxycycline) - results of individual treatments may vary, trial NCT04434144.	risk of hospitalization, 80.6% lower, RR 0.19, $p = 0.23$, treatment 0 of 60 (0.0%), control 2 of 56 (3.6%), NNT 28, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of no recovery, 46.4% lower, RR 0.54, $p < 0.001$, treatment 27 of 60 (45.0%), control 47 of 56 (83.9%), NNT 2.6, mid-recovery day 5.
	recovery time, 15.2% lower, relative time 0.85, $p = 0.07$, treatment 60, control 56.
	risk of no viral clearance, 80.6% lower, RR 0.19, $p = 0.23$, treatment 0 of 60 (0.0%), control 2 of 56 (3.6%), NNT 28, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), primary outcome.
	time to viral-, 4.3% lower, relative time 0.96, $p = 0.23$, treatment 60, control 56.
[de Jesús Ascencio-Montiel], 1/24/2022,	risk of death/hospitalization, 59.0% lower, RR 0.41, p

retrospective, Mexico, North America, peer-reviewed, 10 authors, dosage 6mg days 1-2, this trial uses multiple treatments in the treatment arm (combined with AZ, acetaminophen, aspirin) - results of individual treatments may vary.	< 0.001 , treatment 7,898, control 20,150, adjusted per study, multivariable, primary outcome.
	risk of death/hospitalization, 71.0% lower, RR 0.29, $p < 0.001$, treatment 5,557, control 12,526, adjusted per study, with phone call followup, multivariable.
	risk of death, 15.0% lower, RR 0.85, $p = 0.16$, treatment 101 of 7,898 (1.3%), control 303 of 20,150 (1.5%), NNT 445, unadjusted, excluded in exclusion analyses: unadjusted results with alternate outcome adjusted results showing significant changes with adjustments.
	risk of mechanical ventilation, 9.1% lower, RR 0.91, $p = 0.51$, treatment 77 of 7,898 (1.0%), control 216 of 20,150 (1.1%), NNT 1031, unadjusted, excluded in exclusion analyses: unadjusted results with alternate outcome adjusted results showing significant changes with adjustments.
	risk of hospitalization, 47.6% lower, RR 0.52, $p < 0.001$, treatment 485 of 7,898 (6.1%), control 2,360 of 20,150 (11.7%), NNT 18, unadjusted, excluded in exclusion analyses: unadjusted results with alternate outcome adjusted results showing significant changes with adjustments.
[Elalfy] , 2/16/2021, retrospective, Egypt, Africa, peer-reviewed, 15 authors, dosage 18mg days 1, 4, 7, 10, 13, <90kg 18mg, 90-120kg 24mg, >120kg 30mg, this trial uses multiple treatments in the treatment arm (combined with nitazoxanide, ribavirin, and zinc) - results of individual treatments may vary.	risk of no viral clearance, 86.9% lower, RR 0.13, $p < 0.001$, treatment 7 of 62 (11.3%), control 44 of 51 (86.3%), NNT 1.3, day 15, primary outcome.
	risk of no viral clearance, 58.1% lower, RR 0.42, $p < 0.001$, treatment 26 of 62 (41.9%), control 51 of 51 (100.0%), NNT 1.7, day 7.
[Espitia-Hernandez] , 8/15/2020, retrospective, Mexico, North America, peer-reviewed, mean age 45.1, 5 authors, dosage 6mg days 1-2, 8-9, this trial uses multiple treatments in the treatment arm	recovery time, 70.0% lower, relative time 0.30, $p < 0.001$, treatment 28, control 7.
	risk of viral+ at day 10, 97.2% lower, RR 0.03, $p < 0.001$, treatment 0 of 28 (0.0%), control 7 of 7

(combined with azithromycin and cholecalciferol) - results of individual treatments may vary.	(100.0%), NNT 1.0, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), primary outcome.
[Faisal] , 5/10/2021, Randomized Controlled Trial, Pakistan, South Asia, peer-reviewed, 3 authors, dosage 12mg days 1-5.	risk of no recovery, 68.4% lower, RR 0.32, $p = 0.005$, treatment 6 of 50 (12.0%), control 19 of 50 (38.0%), NNT 3.8, 6-8 days, mid-recovery, primary outcome.
	risk of no recovery, 27.3% lower, RR 0.73, $p = 0.11$, treatment 24 of 50 (48.0%), control 33 of 50 (66.0%), NNT 5.6, 3-5 days.
	risk of no recovery, 75.0% lower, RR 0.25, $p = 0.09$, treatment 2 of 50 (4.0%), control 8 of 50 (16.0%), NNT 8.3, 9-10 days.
[Ghauri] , 12/15/2020, retrospective, Pakistan, South Asia, peer-reviewed, 6 authors, dosage 12mg days 1-6.	risk of fever, 92.2% lower, RR 0.08, $p = 0.04$, treatment 0 of 37 (0.0%), control 7 of 53 (13.2%), NNT 7.6, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 14.
	risk of fever, 86.4% lower, RR 0.14, $p < 0.001$, treatment 2 of 37 (5.4%), control 21 of 53 (39.6%), NNT 2.9, day 10.
	risk of fever, 55.7% lower, RR 0.44, $p < 0.001$, treatment 13 of 37 (35.1%), control 42 of 53 (79.2%), NNT 2.3, day 7.
	risk of fever, 42.2% lower, RR 0.58, $p < 0.001$, treatment 21 of 37 (56.8%), control 52 of 53 (98.1%), NNT 2.4, day 5.
[Krolewiecki] , 6/18/2021, Randomized Controlled Trial, Argentina, South America, peer-reviewed, 23 authors, average treatment delay 3.5 days, dosage 600µg/kg days 1-5, trial NCT004381884.	risk of mechanical ventilation, 151.9% higher, RR 2.52, $p = 1.00$, treatment 1 of 27 (3.7%), control 0 of 14 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm).
	risk of progression, 3.7% higher, RR 1.04, $p = 1.00$, treatment 2 of 27 (7.4%), control 1 of 14 (7.1%).
	viral decay rate, 65.6% lower, RR 0.34, $p = 0.09$, treatment 20, control 14, relative mean viral decay rate (corrigendum table 2), primary outcome.
[Loue] , 4/17/2021, retrospective quasi-randomized (patient choice), France, Europe, peer-reviewed, 2 authors, dosage	risk of death, 70.0% lower, RR 0.30, $p = 0.34$, treatment 1 of 10 (10.0%), control 5 of 15 (33.3%), NNT 4.3.

200µg/kg single dose.	risk of severe case, 55.0% lower, RR 0.45, $p = 0.11$, treatment 3 of 10 (30.0%), control 10 of 15 (66.7%), NNT 2.7.
<p>[López-Medina], 3/4/2021, Double Blind Randomized Controlled Trial, Colombia, South America, peer-reviewed, median age 37.0, 19 authors, average treatment delay 5.0 days, dosage 300µg/kg days 1-5, excluded in exclusion analyses: strong evidence of patients in the control group self-medicating, ivermectin widely used in the population at that time, and the study drug identity was concealed by using the name D11AX22.</p>	<p>risk of death, 66.8% lower, RR 0.33, $p = 0.50$, treatment 0 of 200 (0.0%), control 1 of 198 (0.5%), NNT 198, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).</p>
	<p>risk of escalation of care, 60.8% lower, RR 0.39, $p = 0.11$, treatment 4 of 200 (2.0%), control 10 of 198 (5.1%), NNT 33, odds ratio converted to relative risk.</p>
	<p>risk of escalation of care with post-hoc <12h exclusion, 34.3% lower, RR 0.66, $p = 0.52$, treatment 4 of 200 (2.0%), control 6 of 198 (3.0%), NNT 97, odds ratio converted to relative risk.</p>
	<p>risk of deterioration by ≥ 2 points on an 8-point scale, 43.1% lower, RR 0.57, $p = 0.37$, treatment 4 of 200 (2.0%), control 7 of 198 (3.5%), NNT 65, odds ratio converted to relative risk, primary outcome.</p>
	<p>risk of fever post randomization, 24.8% lower, RR 0.75, $p = 0.38$, treatment 16 of 200 (8.0%), control 21 of 198 (10.6%), NNT 38, odds ratio converted to relative risk.</p>
	<p>risk of unresolved symptoms at day 21, 15.3% lower, RR 0.85, $p = 0.53$, treatment 36 of 200 (18.0%), control 42 of 198 (21.2%), NNT 31, odds ratio converted to relative risk, Cox proportional-hazard model.</p>
<p>[Mahmud], 10/9/2020, Double Blind Randomized Controlled Trial, Bangladesh, South Asia, peer-reviewed, 15 authors, average treatment delay 4.0 days, dosage 12mg single dose, this trial uses multiple treatments in the treatment arm (combined with doxycycline) - results of individual treatments may vary, trial NCT04523831.</p>	<p>risk of death, 85.7% lower, HR 0.14, $p = 0.25$, treatment 0 of 183 (0.0%), control 3 of 183 (1.6%), NNT 61, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).</p>
	<p>risk of progression, 57.0% lower, HR 0.43, $p < 0.001$, treatment 16 of 183 (8.7%), control 32 of 180 (17.8%), NNT 11, adjusted per study, Cox regression.</p>

	risk of no recovery, 94.0% lower, HR 0.06, $p < 0.001$, treatment 72 of 183 (39.3%), control 100 of 180 (55.6%), NNT 6.2, adjusted per study, day 7, Cox regression.
	risk of no recovery, 38.5% lower, RR 0.61, $p = 0.005$, treatment 40 of 183 (21.9%), control 64 of 180 (35.6%), NNT 7.3, day 11.
	risk of no recovery, 96.0% lower, HR 0.04, $p < 0.001$, treatment 42 of 183 (23.0%), control 67 of 180 (37.2%), NNT 7.0, adjusted per study, day 12, Cox regression.
	time to recovery, 27.0% lower, HR 0.73, $p = 0.003$, treatment 183, control 180, Cox regression, primary outcome.
	risk of no viral clearance, 39.0% lower, HR 0.61, $p = 0.002$, treatment 14 of 183 (7.7%), control 36 of 180 (20.0%), NNT 8.1, adjusted per study, Cox regression.
[Manomaipiboon] , 2/2/2022, Double Blind Randomized Controlled Trial, placebo-controlled, Thailand, South Asia, preprint, 8 authors, dosage 12mg days 1-5.	risk of no recovery, 43.5% lower, RR 0.57, $p = 0.26$, treatment 3 of 36 (8.3%), control 6 of 36 (16.7%), NNT 12, adjusted per study, odds ratio converted to relative risk, resolution of symptoms, day 28.
	recovery time, 15.3% lower, RR 0.85, $p = 0.57$, treatment 36, control 36, time to resolution of symptoms.
	risk of no viral clearance, 5.0% lower, RR 0.95, $p = 1.00$, treatment 19 of 36 (52.8%), control 20 of 36 (55.6%), NNT 36, day 14, primary outcome.
	risk of no viral clearance, 3.3% lower, RR 0.97, $p = 1.00$, treatment 29 of 36 (80.6%), control 30 of 36 (83.3%), NNT 36, day 7.
[Mayer] , 9/23/2021, retrospective, Argentina, South America, peer-reviewed, 14 authors, dosage 540µg/kg days 1-5, mean prescribed dose.	risk of death, 55.1% lower, RR 0.45, $p < 0.001$, treatment 3,266, control 17,966, adjusted per study, odds ratio converted to relative risk, Figure 3, multivariable.
	risk of ICU admission, 65.9% lower, RR 0.34, $p < 0.001$, treatment 3,266, control 17,966, adjusted per study, odds ratio converted to relative risk, Figure 3, multivariable.

	risk of death, 27.6% lower, RR 0.72, $p = 0.03$, treatment 3,266, control 17,966, odds ratio converted to relative risk, unadjusted.
	risk of ICU admission, 26.0% lower, RR 0.74, $p = 0.13$, treatment 3,266, control 17,966, odds ratio converted to relative risk, unadjusted.
[Merino], 5/3/2021, retrospective quasi-randomized (patients receiving kit), population-based cohort, Mexico, North America, preprint, 7 authors, dosage 6mg bid days 1-2.	risk of hospitalization, 74.4% lower, RR 0.26, $p < 0.001$, model 7, same time period, patients receiving kit.
	risk of hospitalization, 68.4% lower, RR 0.32, $p < 0.001$, model 1, different time periods, administrative rule.
[Mirahmadizadeh], 6/23/2022, Double Blind Randomized Controlled Trial, placebo-controlled, Iran, Middle East, peer-reviewed, 12 authors, study period 9 April, 2021 - 20 May, 2021, dosage 24mg single dose, 12mg and 24mg arms.	risk of mechanical ventilation, 66.9% lower, RR 0.33, $p = 0.37$, treatment 1 of 131 (0.8%), control 3 of 130 (2.3%), NNT 65, 24mg.
	risk of mechanical ventilation, 33.3% lower, RR 0.67, $p = 1.00$, treatment 2 of 130 (1.5%), control 3 of 130 (2.3%), NNT 130, 12mg.
	risk of hospitalization, 45.9% lower, RR 0.54, $p = 0.22$, treatment 6 of 131 (4.6%), control 11 of 130 (8.5%), NNT 26, 24mg, primary outcome.
	risk of hospitalization, 27.3% lower, RR 0.73, $p = 0.63$, treatment 8 of 130 (6.2%), control 11 of 130 (8.5%), NNT 43, 12mg, primary outcome.
	risk of no recovery, 38.9% lower, RR 0.61, $p = 0.27$, treatment 8 of 131 (6.1%), control 13 of 130 (10.0%), NNT 26, day 28, 24mg.
	risk of no recovery, 30.8% lower, RR 0.69, $p = 0.50$, treatment 9 of 130 (6.9%), control 13 of 130 (10.0%), NNT 32, day 28, 12mg.
[Mohan], 2/2/2021, Double Blind Randomized Controlled Trial, India, South Asia, peer-reviewed, 27 authors, average treatment delay 5.0 days, dosage 400µg/kg single dose, 200µg/kg also tested.	risk of no discharge at day 14, 62.5% lower, RR 0.38, $p = 0.27$, treatment 2 of 40 (5.0%), control 6 of 45 (13.3%), NNT 12, ivermectin 24mg.
	risk of clinical worsening, 32.5% lower, RR 0.68, $p = 0.72$, treatment 3 of 40 (7.5%), control 5 of 45 (11.1%), NNT 28, ivermectin 24mg.
	risk of no viral clearance, 23.8% lower, RR 0.76, $p =$

	0.18, treatment 21 of 40 (52.5%), control 31 of 45 (68.9%), NNT 6.1, ivermectin 24mg, day 5, primary outcome.
	risk of no viral clearance, 10.3% lower, RR 0.90, $p = 0.65$, treatment 20 of 36 (55.6%), control 26 of 42 (61.9%), NNT 16, ivermectin 24mg, day 7.
[Mourya] , 4/1/2021, retrospective, India, South Asia, peer-reviewed, 5 authors, dosage 12mg days 1-7.	risk of no viral clearance, 89.4% lower, RR 0.11, $p < 0.001$, treatment 5 of 50 (10.0%), control 47 of 50 (94.0%), NNT 1.2, primary outcome.
[Ravikirti (B)] , 1/9/2021, Double Blind Randomized Controlled Trial, India, South Asia, peer-reviewed, 11 authors, average treatment delay 6.1 days, dosage 12mg days 1, 2.	risk of death, 88.7% lower, RR 0.11, $p = 0.12$, treatment 0 of 55 (0.0%), control 4 of 57 (7.0%), NNT 14, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of mechanical ventilation, 79.3% lower, RR 0.21, $p = 0.10$, treatment 1 of 55 (1.8%), control 5 of 57 (8.8%), NNT 14.
	risk of ICU admission, 13.6% lower, RR 0.86, $p = 0.80$, treatment 5 of 55 (9.1%), control 6 of 57 (10.5%), NNT 70.
	risk of no hospital discharge, 88.7% lower, RR 0.11, $p = 0.12$, treatment 0 of 55 (0.0%), control 4 of 57 (7.0%), NNT 14, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of no viral clearance, 11.6% higher, RR 1.12, $p = 0.35$, treatment 42 of 55 (76.4%), control 39 of 57 (68.4%).
[Reis] , 8/6/2021, Double Blind Randomized Controlled Trial, Brazil, South America, peer-reviewed, 27 authors, study period 23 March, 2021 - 6 August, 2021, dosage 400µg/kg days 1-3, trial NCT04727424 (TOGETHER), excluded in exclusion analyses: multiple anomalies as per detailed analysis.	risk of death, 12.0% lower, RR 0.88, $p = 0.68$, treatment 21 of 679 (3.1%), control 24 of 679 (3.5%), NNT 226.
	risk of mechanical ventilation, 23.0% lower, RR 0.77, $p = 0.38$, treatment 19 of 679 (2.8%), control 25 of 679 (3.7%), NNT 113.
	risk of hospitalization, 17.0% lower, RR 0.83, $p = 0.19$, treatment 79 of 679 (11.6%), control 95 of 679 (14.0%), NNT 42.
	extended ER observation or hospitalization, 10.0%

	lower, RR 0.90, $p = 0.42$, treatment 100 of 679 (14.7%), control 111 of 679 (16.3%), NNT 62, primary outcome.
	risk of no viral clearance, no change, RR 1.00, $p = 1.00$, treatment 106 of 142 (74.6%), control 123 of 165 (74.5%), day 7.
<p>[Rezai], 6/16/2022, Double Blind Randomized Controlled Trial, placebo-controlled, Iran, Middle East, peer-reviewed, mean age 35.5, 29 authors, study period 19 February, 2021 - 30 August, 2021, dosage 400µg/kg days 1-3, trial IRCT20111224008507N4, excluded in exclusion analyses: multiple critical issues, see study page.</p>	risk of death, 4.9% higher, RR 1.05, $p = 1.00$, treatment 1 of 268 (0.4%), control 1 of 281 (0.4%).
	risk of ICU admission, 9.0% higher, RR 1.09, $p = 0.95$, treatment 268, control 281.
	risk of hospitalization, 36.0% higher, RR 1.36, $p = 0.41$, treatment 268, control 281.
	risk of no recovery, 2.0% higher, RR 1.02, $p = 0.49$, treatment 268, control 281, post-hoc primary outcome.
	risk of no recovery, 13.2% lower, RR 0.87, $p = 0.09$, treatment mean 3.87 (± 0.18) n=268, control mean 4.46 (± 0.18) n=281, cough.
	risk of no recovery, 16.7% lower, RR 0.83, $p = 0.81$, treatment mean 2.5 (± 0.51) n=268, control mean 3.0 (± 0.92) n=281, tachypnea.
	risk of no viral clearance, 23.5% higher, RR 1.23, $p = 0.16$, treatment 268, control 281.
<p>[Rocha], 5/23/2022, Double Blind Randomized Controlled Trial, placebo-controlled, Mexico, North America, preprint, 21 authors, dosage 12mg days 1-3, trial NCT04407507.</p>	risk of progression to serious adverse events, 186.7% higher, RR 2.87, $p = 1.00$, treatment 1 of 30 (3.3%), control 0 of 26 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm).
	viral load, 2.4% lower, relative load 0.98, $p = 0.64$, treatment mean 33.74 (± 4.77) n=30, control mean 32.94 (± 7.74) n=26, day 14.
	viral load, 7.8% lower, relative load 0.92, $p = 0.04$, treatment mean 30.64 (± 3.74) n=30, control mean 28.25 (± 4.21) n=26, day 5.
<p>[Roy], 3/12/2021, retrospective, database analysis, India, South Asia, preprint, 5 authors, dosage not specified, this trial</p>	relative time to clinical response of wellbeing, 5.6% lower, relative time 0.94, $p = 0.87$, treatment 14, control 15, primary outcome.

uses multiple treatments in the treatment arm (combined with doxycycline) - results of individual treatments may vary, excluded in exclusion analyses: no serious outcomes reported and fast recovery in treatment and control groups, there is little room for a treatment to improve results.	
[Szente Fonseca] , 10/31/2020, retrospective, Brazil, South America, peer-reviewed, mean age 50.6, 10 authors, average treatment delay 4.6 days, dosage 12mg days 1-2, excluded in exclusion analyses: result is likely affected by collinearity across treatments in the model.	risk of hospitalization, 13.9% higher, RR 1.14, $p = 0.53$, treatment 340, control 377, adjusted per study, odds ratio converted to relative risk, control prevalence approximated with overall prevalence, primary outcome.
[Vallejos] , 7/2/2021, Double Blind Randomized Controlled Trial, Argentina, South America, peer-reviewed, 29 authors, average treatment delay 4.0 days, dosage 12mg days 1-2, <80kg 12mg, 80-110kg 18mg, >110kg 24mg.	risk of death, 33.5% higher, RR 1.33, $p = 0.70$, treatment 4 of 250 (1.6%), control 3 of 251 (1.2%), odds ratio converted to relative risk.
	risk of mechanical ventilation, 33.5% higher, RR 1.33, $p = 0.70$, treatment 4 of 250 (1.6%), control 3 of 251 (1.2%), odds ratio converted to relative risk.
	risk of hospitalization, 33.0% lower, RR 0.67, $p = 0.23$, treatment 14 of 250 (5.6%), control 21 of 251 (8.4%), NNT 36, odds ratio converted to relative risk, primary outcome.
	risk of no viral clearance, 5.0% higher, RR 1.05, $p = 0.55$, treatment 137 of 250 (54.8%), control 131 of 251 (52.2%), odds ratio converted to relative risk, day 3.
	risk of no viral clearance, 26.8% higher, RR 1.27, $p = 0.29$, treatment 38 of 250 (15.2%), control 30 of 251 (12.0%), odds ratio converted to relative risk, day 12.

Late treatment.

Effect extraction follows pre-specified rules as detailed above and gives priority to more serious outcomes. Only the first (most serious) outcome is used in pooled analysis, which may differ from the effect a paper focuses on. Other outcomes are used in outcome specific analyses.

[Abd-El salam] , 6/2/2021, Randomized Controlled Trial, Egypt, Africa, peer-reviewed, 16 authors, dosage 12mg days 1-3.	risk of death, 25.0% lower, RR 0.75, $p = 0.70$, treatment 3 of 82 (3.7%), control 4 of 82 (4.9%), NNT 82, odds ratio converted to relative risk, logistic regression, primary outcome.
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	<p>risk of mechanical ventilation, no change, RR 1.00, $p = 1.00$, treatment 3 of 82 (3.7%), control 3 of 82 (3.7%).</p> <p>hospitalization time, 19.6% lower, relative time 0.80, $p = 0.09$, treatment 82, control 82.</p>
<p>[Ahsan], 4/29/2021, retrospective, Pakistan, South Asia, peer-reviewed, 10 authors, dosage 150µg/kg days 1-2, 150-200µg/kg, this trial uses multiple treatments in the treatment arm (combined with doxycycline) - results of individual treatments may vary, excluded in exclusion analyses: unadjusted results with no group details.</p>	<p>risk of death, 50.0% lower, RR 0.50, $p = 0.03$, treatment 17 of 110 (15.5%), control 17 of 55 (30.9%), NNT 6.5.</p>
<p>[Baguma], 12/28/2021, retrospective, Uganda, Africa, preprint, 16 authors, study period March 2020 - October 2021, dosage not specified.</p>	<p>risk of death, 96.8% lower, RR 0.03, $p = 0.31$, treatment 7, control 474, adjusted per study, odds ratio converted to relative risk, multivariable, control prevalence approximated with overall prevalence.</p>
<p>[Beltran Gonzalez], 2/23/2021, Double Blind Randomized Controlled Trial, Mexico, North America, peer-reviewed, mean age 53.8, 13 authors, average treatment delay 7.0 days, dosage 12mg single dose, 18mg for patients >80kg, excluded in exclusion analyses: major inconsistencies reported and the data is no longer available, although the authors state that it is available, and have shared it with an anti-treatment group.</p>	<p>risk of death, 14.4% lower, RR 0.86, $p = 1.00$, treatment 5 of 36 (13.9%), control 6 of 37 (16.2%), NNT 43.</p>
	<p>risk of respiratory deterioration or death, 8.6% lower, RR 0.91, $p = 1.00$, treatment 8 of 36 (22.2%), control 9 of 37 (24.3%), NNT 48.</p>
	<p>risk of no hospital discharge, 37.0% higher, RR 1.37, $p = 0.71$, treatment 4 of 36 (11.1%), control 3 of 37 (8.1%).</p> <p>hospitalization time, 20.0% higher, relative time 1.20, $p = 0.43$, treatment 36, control 37, primary outcome.</p>
<p>[Budhiraja], 11/18/2020, retrospective, India, South Asia, preprint, 12 authors, dosage not specified.</p>	<p>risk of death, 99.1% lower, RR 0.009, $p = 0.04$, treatment 0 of 34 (0.0%), control 103 of 942 (10.9%), NNT 9.1, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), unadjusted, primary outcome.</p>
<p>[Camprubi], 11/11/2020, retrospective, Spain, Europe, peer-reviewed, 9 authors, average treatment delay 12.0 days, dosage 200µg/kg single dose.</p>	<p>risk of mechanical ventilation, 40.0% lower, RR 0.60, $p = 0.67$, treatment 3 of 13 (23.1%), control 5 of 13 (38.5%), NNT 6.5.</p>
	<p>risk of ICU admission, 33.3% lower, RR 0.67, $p = 1.00$, treatment 2 of 13 (15.4%), control 3 of 13 (23.1%),</p>

	NNT 13, ICU at day 8.
	risk of no improvement at day 8, 33.3% higher, RR 1.33, $p = 1.00$, treatment 4 of 13 (30.8%), control 3 of 13 (23.1%).
	risk of no viral clearance, 25.0% higher, RR 1.25, $p = 1.00$, treatment 5 of 13 (38.5%), control 4 of 13 (30.8%), tests done between days 3-5, primary outcome.
[Chachar] , 9/30/2020, Randomized Controlled Trial, India, South Asia, peer-reviewed, 6 authors, dosage 36mg, 12mg stat, 12mg after 12 hours, 12mg after 24 hours.	risk of no recovery at day 7, 10.0% lower, RR 0.90, $p = 0.50$, treatment 9 of 25 (36.0%), control 10 of 25 (40.0%), NNT 25, primary outcome.
[Efimenko] , 2/28/2022, retrospective, propensity score matching, USA, North America, peer-reviewed, 6 authors, study period 1 January, 2020 - 11 July, 2021, dosage not specified, this trial compares with another treatment - results may be better when compared to placebo.	risk of death, 69.2% lower, OR 0.31, $p < 0.001$, treatment 1,072, control 40,536, propensity score matching, RR approximated with OR.
[Elavarasi] , 8/12/2021, retrospective, India, South Asia, preprint, 26 authors, dosage not specified, excluded in exclusion analyses: unadjusted results with no group details.	risk of death, 19.6% lower, RR 0.80, $p = 0.12$, treatment 48 of 283 (17.0%), control 311 of 1,475 (21.1%), NNT 24, unadjusted.
[Ferreira] , 11/26/2021, retrospective, Brazil, South America, peer-reviewed, 5 authors, study period 12 March, 2020 - 8 July, 2020, average treatment delay 7.0 days, dosage not specified, excluded in exclusion analyses: unadjusted results with no group details, substantial unadjusted confounding by indication likely.	risk of death, 5.0% higher, RR 1.05, $p = 1.00$, treatment 3 of 21 (14.3%), control 11 of 81 (13.6%).
	risk of death/intubation, 54.3% higher, RR 1.54, $p = 0.37$, treatment 6 of 21 (28.6%), control 15 of 81 (18.5%).
	risk of death/intubation/ICU, 62.4% higher, RR 1.62, $p = 0.27$, treatment 8 of 21 (38.1%), control 19 of 81 (23.5%).
[George] , 5/27/2022, Randomized Controlled Trial, India, South Asia, peer-reviewed, 15 authors, study period June 2020 - February 2021, dosage 24mg single dose, trial CTRI/2020/05/025068.	risk of death, 30.4% lower, RR 0.70, $p = 0.55$, treatment 5 of 35 (14.3%), control 8 of 39 (20.5%), NNT 16, 24mg.
	risk of death, 2.6% higher, RR 1.03, $p = 1.00$, treatment 8 of 38 (21.1%), control 8 of 39 (20.5%), 12mg.

	recovery time, 18.7% lower, relative time 0.81, $p = 0.37$, treatment mean 4.82 (± 4.35) $n=35$, control mean 5.93 (± 5.93) $n=39$, 24mg.
	recovery time, 6.2% lower, relative time 0.94, $p = 0.78$, treatment mean 5.56 (± 5.42) $n=38$, control mean 5.93 (± 5.93) $n=39$, 12mg.
	risk of progression, 33.1% lower, RR 0.67, $p = 0.41$, treatment 6 of 35 (17.1%), control 10 of 39 (25.6%), NNT 12, 24mg.
	risk of progression, 17.9% lower, RR 0.82, $p = 0.79$, treatment 8 of 38 (21.1%), control 10 of 39 (25.6%), NNT 22, 12mg.
<p>[Gorial], 7/8/2020, retrospective, Iraq, Middle East, preprint, 9 authors, dosage 200μg/kg single dose.</p>	<p>risk of death, 71.0% lower, RR 0.29, $p = 1.00$, treatment 0 of 16 (0.0%), control 2 of 71 (2.8%), NNT 36, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).</p>
	hospitalization time, 42.0% lower, relative time 0.58, $p < 0.001$, treatment 16, control 71.
	risk of no recovery, 71.0% lower, RR 0.29, $p = 1.00$, treatment 0 of 16 (0.0%), control 2 of 71 (2.8%), NNT 36, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), primary outcome.
<p>[Hashim], 10/26/2020, Single Blind Randomized Controlled Trial, Iraq, Middle East, peer-reviewed, 7 authors, dosage 200μg/kg days 1-2, some patients received a third dose on day 8, this trial uses multiple treatments in the treatment arm (combined with doxycycline) - results of individual treatments may vary, trial NCT04591600.</p>	<p>risk of death, 91.7% lower, RR 0.08, $p = 0.03$, treatment 0 of 59 (0.0%), control 6 of 70 (8.6%), NNT 12, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), excluding non-randomized critical patients, primary outcome.</p>
	risk of death, 67.1% lower, RR 0.33, $p = 0.16$, treatment 2 of 70 (2.9%), control 6 of 70 (8.6%), NNT 18, odds ratio converted to relative risk, including critical patients that were always allocated to treatment.
	risk of progression, 83.1% lower, RR 0.17, $p = 0.07$, treatment 1 of 59 (1.7%), control 7 of 70 (10.0%), NNT 12, excluding non-randomized critical patients.
	risk of progression, 57.4% lower, RR 0.43, $p = 0.20$,

	treatment 3 of 70 (4.3%), control 7 of 70 (10.0%), NNT 18, odds ratio converted to relative risk, including critical patients that were always allocated to treatment.
	recovery time, 40.7% lower, relative time 0.59, $p < 0.001$, treatment 70, control 70.
<p>[Hazan], 7/7/2021, retrospective, USA, North America, preprint, 7 authors, average treatment delay 9.2 days, dosage 12mg days 1, 4, 8, this trial uses multiple treatments in the treatment arm (combined with doxycycline, zinc, vitamin D, vitamin C) - results of individual treatments may vary, excluded in exclusion analyses: study uses a synthetic control arm.</p>	<p>risk of death, 86.2% lower, RR 0.14, $p = 0.04$, NNT 6.9, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).</p>
	<p>risk of hospitalization, 93.5% lower, RR 0.07, $p = 0.001$, NNT 3.3, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), primary outcome.</p>
<p>[Huvemek], 3/25/2021, Double Blind Randomized Controlled Trial, Bulgaria, Europe, preprint, 1 author, average treatment delay 7.0 days, dosage 400µg/kg days 1-3.</p>	<p>risk of no improvement, 31.6% lower, RR 0.68, $p = 0.28$, treatment 13 of 50 (26.0%), control 19 of 50 (38.0%), NNT 8.3, day 7, patients with improvement on WHO scale.</p>
	<p>risk of no improvement, 34.5% lower, RR 0.66, $p = 0.07$, treatment 19 of 50 (38.0%), control 29 of 50 (58.0%), NNT 5.0, day 4, patients with improvement on WHO scale.</p>
<p>[Jamir], 12/13/2021, retrospective, India, South Asia, peer-reviewed, 6 authors, study period June 2020 - October 2010, dosage not specified.</p>	<p>risk of death, 53.0% higher, RR 1.53, $p = 0.13$, treatment 32 of 76 (42.1%), control 69 of 190 (36.3%), adjusted per study, multivariable Cox regression.</p>
<p>[Khan], 9/24/2020, retrospective, Bangladesh, South Asia, preprint, median age 35.0, 8 authors, dosage 12mg single dose.</p>	<p>risk of death, 87.1% lower, RR 0.13, $p = 0.02$, treatment 1 of 115 (0.9%), control 9 of 133 (6.8%), NNT 17.</p>
	<p>risk of ICU admission, 89.5% lower, RR 0.11, $p = 0.007$, treatment 1 of 115 (0.9%), control 11 of 133 (8.3%), NNT 14.</p>
	<p>risk of progression, 83.5% lower, RR 0.17, $p < 0.001$, treatment 3 of 115 (2.6%), control 21 of 133 (15.8%), NNT 7.6.</p>
	<p>risk of no recovery, 87.1% lower, RR 0.13, $p = 0.02$, treatment 1 of 115 (0.9%), control 9 of 133 (6.8%), NNT 17.</p>

	hospitalization time, 40.0% lower, relative time 0.60, $p < 0.001$, treatment 115, control 133.
	time to viral-, 73.3% lower, relative time 0.27, $p < 0.001$, treatment 115, control 133.
<p>[Kishoria], 8/31/2020, Randomized Controlled Trial, India, South Asia, peer-reviewed, 7 authors, dosage 12mg single dose, excluded in exclusion analyses: excessive unadjusted differences between groups.</p>	<p>risk of no hospital discharge, 7.5% higher, RR 1.08, $p = 1.00$, treatment 11 of 19 (57.9%), control 7 of 13 (53.8%).</p>
	<p>risk of no viral clearance, 7.5% higher, RR 1.08, $p = 1.00$, treatment 11 of 19 (57.9%), control 7 of 13 (53.8%), day 3, primary outcome.</p>
	<p>risk of no viral clearance, 220.0% higher, RR 3.20, $p = 0.45$, treatment 1 of 5 (20.0%), control 0 of 6 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm), day 5.</p>
<p>[Lim], 11/3/2021, Randomized Controlled Trial, Malaysia, Europe, peer-reviewed, 26 authors, study period 31 May, 2021 - 9 October, 2021, average treatment delay 5.1 days, dosage 400µg/kg days 1-5, trial NCT04920942 (I-TECH).</p>	<p>risk of death, 69.0% lower, RR 0.31, $p = 0.09$, treatment 3 of 241 (1.2%), control 10 of 249 (4.0%), NNT 36.</p>
	<p>risk of death, 75.2% lower, RR 0.25, $p = 0.02$, treatment 3 of 52 (5.8%), control 10 of 43 (23.3%), NNT 5.7, among patients progressing to severe cases (mostly before treatment ended).</p>
	<p>risk of mechanical ventilation, 59.0% lower, RR 0.41, $p = 0.17$, treatment 4 of 241 (1.7%), control 10 of 249 (4.0%), NNT 42.</p>
	<p>risk of ICU admission, 22.0% lower, RR 0.78, $p = 0.79$, treatment 6 of 241 (2.5%), control 8 of 249 (3.2%), NNT 138.</p>
	<p>risk of progression, 31.1% lower, RR 0.69, $p = 0.29$, treatment 14 of 241 (5.8%), control 21 of 249 (8.4%), NNT 38, death/IMV/NIV/high flow (WHO severe cases).</p>
	<p>risk of progression, 25.0% higher, RR 1.25, $p = 0.25$, treatment 52 of 241 (21.6%), control 43 of 249 (17.3%), primary outcome.</p>
	<p>hospitalization time, 5.5% higher, relative time 1.05, $p = 0.38$, treatment 241, control 249.</p>
	<p>risk of no recovery, 2.5% higher, RR 1.02, $p = 0.86$,</p>

	treatment 116 of 241 (48.1%), control 116 of 247 (47.0%), day 5.
<p>[Lima-Morales], 2/10/2021, prospective, Mexico, North America, peer-reviewed, 9 authors, average treatment delay 7.2 days, dosage 12mg single dose, this trial uses multiple treatments in the treatment arm (combined with azithromycin, montelukast, and aspirin) - results of individual treatments may vary.</p>	<p>risk of death, 77.7% lower, RR 0.22, $p < 0.001$, treatment 15 of 481 (3.1%), control 52 of 287 (18.1%), NNT 6.7, adjusted per study, odds ratio converted to relative risk, multivariate.</p>
	<p>risk of mechanical ventilation, 51.9% lower, RR 0.48, $p = 0.15$, treatment 8 of 434 (1.8%), control 11 of 287 (3.8%), NNT 50.</p>
	<p>risk of hospitalization, 67.4% lower, RR 0.33, $p < 0.001$, treatment 44 of 481 (9.1%), control 89 of 287 (31.0%), NNT 4.6, adjusted per study, odds ratio converted to relative risk, multivariate.</p>
	<p>risk of no recovery, 58.6% lower, RR 0.41, $p < 0.001$, treatment 75 of 481 (15.6%), control 118 of 287 (41.1%), NNT 3.9, adjusted per study, odds ratio converted to relative risk, recovery at day 14 after symptoms, multivariate.</p>
<p>[Mustafa], 12/29/2021, retrospective, Pakistan, South Asia, peer-reviewed, 7 authors, dosage varies, excluded in exclusion analyses: unadjusted results with no group details.</p>	<p>risk of death, 63.7% lower, RR 0.36, $p = 0.09$, treatment 3 of 73 (4.1%), control 42 of 371 (11.3%), NNT 14.</p>
<p>[Naggie], 6/12/2022, Double Blind Randomized Controlled Trial, placebo-controlled, USA, North America, preprint, mean age 48.0, 1 author, study period 15 December, 2021 - 1 February, 2022, average treatment delay 6.0 days, dosage 400µg/kg days 1-3, trial NCT04885530 (ACTIV-6).</p>	<p>risk of death, 194.7% higher, RR 2.95, $p = 1.00$, treatment 1 of 817 (0.1%), control 0 of 774 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm), day 28.</p>
	<p>risk of hospitalization, 5.3% higher, RR 1.05, $p = 1.00$, treatment 10 of 817 (1.2%), control 9 of 774 (1.2%), day 28.</p>
	<p>risk of progression, 68.4% lower, RR 0.32, $p = 0.36$, treatment 1 of 817 (0.1%), control 3 of 774 (0.4%), NNT 377, aggravated C19 pneumonia, eTable 2.</p>
	<p>risk of progression, 5.3% lower, RR 0.95, $p = 1.00$, treatment 4 of 817 (0.5%), control 4 of 774 (0.5%), NNT 3676, C19 pneumonia, eTable 2.</p>
	<p>risk of progression, 20.0% higher, RR 1.20, $p = 0.32$, treatment 32 of 817 (3.9%), control 28 of 774 (3.6%), adjusted per study, urgent or emergency care visits,</p>

	hospitalizations, or death.
	clinical progression, 24.0% lower, OR 0.76, $p = 0.07$, treatment 817, control 774, mid-recovery, day 7, RR approximated with OR.
	clinical progression, 27.0% lower, OR 0.73, $p = 0.05$, treatment 817, control 774, day 14, RR approximated with OR.
	clinical progression, 10.0% lower, OR 0.90, $p = 0.57$, treatment 817, control 774, day 28, RR approximated with OR.
	risk of no recovery, 6.5% lower, HR 0.93, $p = 0.18$, treatment 817, control 774, post-hoc primary outcome.
	risk of no recovery, 44.1% lower, HR 0.56, $p = 0.03$, treatment 39, control 51, severe.
	risk of no recovery, 2.9% lower, HR 0.97, $p = 0.80$, treatment 247, control 221, moderate.
	risk of no recovery, 10.7% lower, HR 0.89, $p = 0.12$, treatment 434, control 490, mild.
	risk of no recovery, 22.0% higher, HR 1.22, $p = 0.33$, treatment 54, control 55, no symptoms.
	risk of no recovery, 5.7% lower, HR 0.94, $p = 0.62$, onset 3 days.
	risk of no recovery, 13.8% lower, HR 0.86, $p = 0.03$, onset 5 days.
	risk of no recovery, 12.3% lower, HR 0.88, $p = 0.08$, onset 7 days.
	risk of no recovery, no change, HR 1.00, $p = 1.00$, onset 9 days.
	risk of no recovery, 16.3% higher, HR 1.16, $p = 0.40$, onset 11 days.
	risk of no recovery, 35.1% higher, HR 1.35, $p = 0.28$, onset 13 days.
[Okumuş], 1/12/2021, Double Blind	risk of death, 33.3% lower, RR 0.67, $p = 0.55$,

Randomized Controlled Trial, Turkey, Europe, peer-reviewed, 15 authors, dosage 200µg/kg days 1-5, 36-50kg - 9mg, 51-65kg - 12mg, 66-79kg - 15mg, >80kg 200µg/kg, trial NCT04646109.	treatment 6 of 30 (20.0%), control 9 of 30 (30.0%), NNT 10.
	risk of no improvement at day 10, 42.9% lower, RR 0.57, $p = 0.18$, treatment 8 of 30 (26.7%), control 14 of 30 (46.7%), NNT 5.0.
	risk of no improvement at day 5, 15.8% lower, RR 0.84, $p = 0.60$, treatment 16 of 30 (53.3%), control 19 of 30 (63.3%), NNT 10, primary outcome.
	risk of no viral clearance, 80.0% lower, RR 0.20, $p = 0.02$, treatment 2 of 16 (12.5%), control 5 of 8 (62.5%), NNT 2.0, day 10.
[Ozer] , 11/23/2021, prospective, USA, North America, peer-reviewed, 12 authors, dosage 200µg/kg days 1, 3.	risk of death, 75.0% lower, RR 0.25, $p = 0.09$, treatment 2 of 60 (3.3%), control 8 of 60 (13.3%), NNT 10.0, PSM.
	risk of mechanical ventilation, 12.6% lower, RR 0.87, $p = 0.20$, treatment 3 of 60 (5.0%), control 2 of 60 (3.3%), odds ratio converted to relative risk, PSM, multivariable.
	ventilation time, 83.3% lower, relative time 0.17, $p = 0.002$, treatment 60, control 60.
	risk of ICU admission, 48.7% lower, RR 0.51, $p = 0.42$, treatment 6 of 60 (10.0%), control 3 of 60 (5.0%), odds ratio converted to relative risk, PSM, multivariable.
	ICU time, 70.6% lower, relative time 0.29, $p < 0.001$, treatment 60, control 60.
	hospitalization time, 9.0% higher, relative time 1.09, $p = 0.09$, treatment 60, control 60, PSM, multivariable.
[Podder] , 9/3/2020, Randomized Controlled Trial, Bangladesh, South Asia, peer-reviewed, 4 authors, average treatment delay 7.0 days, dosage 200µg/kg single dose.	recovery time from enrollment, 16.1% lower, relative time 0.84, $p = 0.34$, treatment 32, control 30.
[Pott-Junior] , 3/9/2021, Randomized Controlled Trial, Brazil, South America, peer-reviewed, 10 authors, average	risk of mechanical ventilation, 85.2% lower, RR 0.15, $p = 0.25$, treatment 1 of 27 (3.7%), control 1 of 4 (25.0%), NNT 4.7.
	risk of ICU admission, 85.2% lower, RR 0.15, $p = 0.25$,

treatment delay 8.0 days, dosage 200µg/kg single dose, dose varies in three arms 100, 200, 400µg/kg, trial NCT04431466.	treatment 1 of 27 (3.7%), control 1 of 4 (25.0%), NNT 4.7.
	relative improvement in Ct value, 0.8% better, RR 0.99, $p = 1.00$, treatment 27, control 3.
	risk of no viral clearance, 11.1% higher, RR 1.11, $p = 1.00$, treatment 10 of 27 (37.0%), control 1 of 3 (33.3%), primary outcome.
[Rajter] , 10/13/2020, retrospective, propensity score matching, USA, North America, peer-reviewed, 6 authors, dosage 200µg/kg single dose.	risk of death, 46.0% lower, RR 0.54, $p = 0.045$, treatment 13 of 98 (13.3%), control 24 of 98 (24.5%), NNT 8.9, adjusted per study, odds ratio converted to relative risk, PSM.
	risk of death, 66.9% lower, RR 0.33, $p = 0.03$, treatment 26 of 173 (15.0%), control 27 of 107 (25.2%), NNT 9.8, adjusted per study, odds ratio converted to relative risk, multivariate, primary outcome.
	risk of mechanical ventilation, 63.6% lower, RR 0.36, $p = 0.10$, treatment 4 of 98 (4.1%), control 11 of 98 (11.2%), NNT 14, matched cohort excluding intubated at baseline.
[Ravikirti] , 4/6/2022, retrospective, India, South Asia, preprint, 7 authors, study period 1 April, 2021 - 15 May, 2021, dosage varies, excluded in exclusion analyses: exclusion of patients in less severe condition, data/analysis concerns.	risk of death, 2.8% lower, RR 0.97, $p = 0.82$, treatment 53 of 171 (31.0%), control 254 of 794 (32.0%), NNT 100, odds ratio converted to relative risk.
[Rezai (B)] , 6/16/2022, Double Blind Randomized Controlled Trial, placebo-controlled, Iran, Middle East, peer-reviewed, mean age 53.8, 29 authors, study period 19 February, 2021 - 14 August, 2021, average treatment delay 7.18 days, dosage 400µg/kg days 1-3, trial IRCT20111224008507N5, excluded in exclusion analyses: multiple critical issues, see study page.	risk of death, 30.8% lower, RR 0.69, $p = 0.36$, treatment 13 of 311 (4.2%), control 18 of 298 (6.0%), NNT 54.
	risk of mechanical ventilation, 50.0% lower, RR 0.50, $p = 0.07$, treatment 311, control 298.
	risk of ICU admission, 16.0% lower, RR 0.84, $p = 0.47$, treatment 311, control 298.
	hospitalization time, 11.5% higher, relative time 1.11, $p = 0.009$, treatment mean 7.98 (± 4.4) $n=311$, control mean 7.16 (± 3.2) $n=298$.
	deterioration, 12.7% higher, RR 1.13, $p = 0.74$, treatment 20 of 311 (6.4%), control 17 of 298 (5.7%).

	risk of no recovery, 24.2% lower, RR 0.76, $p = 0.02$, treatment 311, control 298, post-hoc primary outcome.
	risk of no recovery, 64.0% lower, RR 0.36, $p = 0.06$, treatment 5 of 145 (3.4%), control 10 of 105 (9.5%), NNT 16, day 7, cough.
	risk of no recovery, 76.0% lower, RR 0.24, $p = 0.38$, day 7, tachypnea.
[Rezk], 10/30/2021, prospective, Egypt, Africa, peer-reviewed, 4 authors, dosage 36mg days 1, 3, 6.	risk of death, 80.0% lower, RR 0.20, $p = 0.50$, treatment 0 of 160 (0.0%), control 2 of 160 (1.2%), NNT 80, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of progression, 55.6% lower, RR 0.44, $p = 0.06$, treatment 8 of 160 (5.0%), control 18 of 160 (11.2%), NNT 16, 2 weeks, including deaths.
	risk of no recovery, 33.4% lower, RR 0.67, $p = 0.27$, treatment 14 of 145 (9.7%), control 20 of 138 (14.5%), NNT 21, 4 weeks, more patients were lost to followup in the control group.
	time to viral-, 27.3% lower, relative time 0.73, $p = 0.01$, treatment 160, control 160.
[Shahbaznejad], 1/19/2021, Double Blind Randomized Controlled Trial, Iran, Middle East, peer-reviewed, 8 authors, average treatment delay 6.29 days, dosage 200µg/kg single dose.	risk of death, 197.1% higher, RR 2.97, $p = 1.00$, treatment 1 of 35 (2.9%), control 0 of 34 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm), patient died within 24 hours of admission.
	risk of mechanical ventilation, 94.3% higher, RR 1.94, $p = 1.00$, treatment 2 of 35 (5.7%), control 1 of 34 (2.9%).
	recovery time, 31.6% lower, relative time 0.68, $p = 0.048$, treatment 35, control 34, duration of dsypnea.
	recovery time, 19.2% lower, relative time 0.81, $p = 0.02$, treatment 35, control 34, duration of all symptoms, primary outcome.
	hospitalization time, 15.5% lower, relative time 0.85, $p = 0.02$, treatment 35, control 34.

<p>[Shimizu], 12/31/2021, retrospective, Japan, Asia, peer-reviewed, 11 authors, study period December 2020 - May 2021, dosage 200µg/kg days 1, 14.</p>	<p>risk of death, 99.9% lower, HR 0.001, $p < 0.001$, treatment 0 of 39 (0.0%), control 8 of 49 (16.3%), NNT 6.1, adjusted per study, Cox proportional hazard regression.</p>
	<p>ventilator free days, 47.9% lower, OR 0.52, $p = 0.03$, treatment 39, control 49, adjusted per study, proportional odds logistic regression, primary outcome, RR approximated with OR.</p>
	<p>ventilation time, 38.5% lower, relative time 0.62, $p < 0.001$, treatment 39, control 49.</p>
	<p>ICU free days, 42.8% lower, OR 0.57, $p = 0.06$, treatment 39, control 49, adjusted per study, proportional odds logistic regression, RR approximated with OR.</p>
	<p>ICU time, 37.5% lower, relative time 0.62, $p < 0.001$, treatment 39, control 49.</p>
	<p>GI complications while ventilated, 77.9% lower, RR 0.22, $p = 0.03$, treatment 39, control 49, adjusted per study, Cox proportional hazard regression.</p>
<p>[Soto], 3/2/2022, retrospective, Peru, South America, peer-reviewed, median age 58.0, 10 authors, study period April 2020 - August 2020, dosage not specified, excluded in exclusion analyses: substantial unadjusted confounding by indication likely, substantial confounding by time possible due to significant changes in SOC and treatment propensity near the start of the pandemic.</p>	<p>risk of death, 41.0% higher, HR 1.41, $p = 0.001$, treatment 280 of 484 (57.9%), control 374 of 934 (40.0%), adjusted per study, multivariable.</p>
<p>[Soto-Becerra], 10/8/2020, retrospective, database analysis, Peru, South America, preprint, median age 59.4, 4 authors, study period 1 April, 2020 - 19 July, 2020, dosage 200µg/kg single dose, excluded in exclusion analyses: substantial unadjusted confounding by indication likely, includes PCR+ patients that may be asymptomatic for COVID-19 but in hospital for other reasons.</p>	<p>risk of death, 17.1% lower, HR 0.83, $p = 0.01$, treatment 92 of 203 (45.3%), control 1,438 of 2,630 (54.7%), NNT 11, IVM vs. control day 43 (last day available) weighted KM from figure 3, per the pre-specified rules, the last available day mortality results have priority.</p>
	<p>risk of death, 39.0% higher, HR 1.39, $p = 0.16$, treatment 47 of 203 (23.2%), control 401 of 2,630 (15.2%), adjusted per study, day 30, Table 2, IVM wHR, primary outcome.</p>
<p>[Spoorthi], 11/14/2020, prospective, India,</p>	<p>recovery time, 21.1% lower, relative time 0.79, $p =$</p>

South Asia, peer-reviewed, 2 authors, dosage not specified, this trial uses multiple treatments in the treatment arm (combined with doxycycline) - results of individual treatments may vary.	0.03, treatment 50, control 50.
	hospitalization time, 15.5% lower, relative time 0.84, $p = 0.01$, treatment 50, control 50.
[Thairu], 2/25/2022, retrospective, Nigeria, Africa, preprint, 5 authors, study period April 2021 - November 2021, dosage 200µg/kg days 1-5, excluded in exclusion analyses: significant confounding by time possible due to separation of groups in different time periods.	risk of death, 87.9% lower, RR 0.12, $p = 0.12$, treatment 0 of 21 (0.0%), control 4 of 26 (15.4%), NNT 6.5, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), propensity score matching.
	risk of death, 93.0% lower, RR 0.07, $p = 0.007$, treatment 0 of 61 (0.0%), control 4 of 26 (15.4%), NNT 6.5, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), all patients.
	time to discharge, 54.6% lower, relative time 0.45, $p < 0.001$, treatment 61, control 26, propensity score matching.
	risk of no viral clearance, 94.8% lower, RR 0.05, $p = 0.001$, treatment 0 of 21 (0.0%), control 10 of 26 (38.5%), NNT 2.6, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), propensity score matching, day 21.
	risk of no viral clearance, 95.2% lower, RR 0.05, $p < 0.001$, treatment 1 of 21 (4.8%), control 26 of 26 (100.0%), NNT 1.1, propensity score matching, day 14.
	risk of no viral clearance, 28.6% lower, RR 0.71, $p = 0.005$, treatment 15 of 21 (71.4%), control 26 of 26 (100.0%), NNT 3.5, propensity score matching, day 5.
[Zubair], 1/18/2022, retrospective, Pakistan, South Asia, peer-reviewed, 8 authors, study period October 2020 - February 2021, dosage 12mg single dose, excluded in exclusion analyses: substantial unadjusted confounding by indication likely, unadjusted results with no group details.	risk of death, 9.0% higher, RR 1.09, $p = 1.00$, treatment 5 of 90 (5.6%), control 5 of 98 (5.1%), unadjusted.
	hospitalization time, 8.0% higher, relative time 1.08, $p = 0.40$, treatment 90, control 98, unadjusted, Table 3, mean number of days.

Effect extraction follows pre-specified rules as detailed above and gives priority to more serious outcomes. Only the first (most serious) outcome is used in pooled analysis, which may differ from the effect a paper focuses on. Other outcomes are used in outcome specific analyses.

[Alam] , 12/15/2020, prospective, Bangladesh, South Asia, peer-reviewed, 13 authors, dosage 12mg monthly.	risk of case, 90.6% lower, RR 0.09, $p < 0.001$, treatment 4 of 58 (6.9%), control 44 of 60 (73.3%), NNT 1.5.
[Behera (B)] , 2/15/2021, prospective, India, South Asia, peer-reviewed, 14 authors, dosage 300µg/kg days 1, 4.	risk of case, 83.0% lower, RR 0.17, $p < 0.001$, treatment 45 of 2,199 (2.0%), control 133 of 1,147 (11.6%), NNT 10, two doses, primary outcome.
[Behera] , 11/3/2020, retrospective, India, South Asia, peer-reviewed, 13 authors, dosage 300µg/kg days 1, 4.	risk of case, 53.8% lower, RR 0.46, $p < 0.001$, treatment 41 of 117 (35.0%), control 145 of 255 (56.9%), NNT 4.6, adjusted per study, odds ratio converted to relative risk, model 2 2+ doses conditional logistic regression.
[Bernigaud] , 11/28/2020, retrospective, France, Europe, peer-reviewed, 12 authors, dosage 200µg/kg days 1, 8, 15, 400µg/kg days 1, 8, 15, two different dosages.	risk of death, 99.4% lower, RR 0.006, $p = 0.08$, treatment 0 of 69 (0.0%), control 150 of 3,062 (4.9%), NNT 20, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of case, 55.1% lower, RR 0.45, $p = 0.01$, treatment 7 of 69 (10.1%), control 692 of 3,062 (22.6%), NNT 8.0.
[Carvallo] , 11/17/2020, prospective, Argentina, South America, peer-reviewed, 4 authors, dosage 12mg weekly, this trial uses multiple treatments in the treatment arm (combined with iota-carrageenan) - results of individual treatments may vary, excluded in exclusion analyses: concern about potential data issues.	risk of case, 99.9% lower, RR 0.001, $p < 0.001$, treatment 0 of 788 (0.0%), control 237 of 407 (58.2%), NNT 1.7, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
[Carvallo (B)] , 10/19/2020, prospective, Argentina, South America, preprint, 1 author, dosage 1mg days 1-14, this trial uses multiple treatments in the treatment arm (combined with iota-carrageenan) - results of individual treatments may vary, excluded in exclusion analyses: concern about potential data issues.	risk of case, 96.3% lower, RR 0.04, $p < 0.001$, treatment 0 of 131 (0.0%), control 11 of 98 (11.2%), NNT 8.9, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
[Chahla (B)] , 1/11/2021, Randomized Controlled Trial, Argentina, South America, peer-reviewed, 11 authors, dosage 12mg	risk of moderate/severe case, 95.2% lower, RR 0.05, $p = 0.002$, treatment 0 of 117 (0.0%), control 10 of 117 (8.5%), NNT 12, relative risk is not 0 because of

<p>weekly, this trial uses multiple treatments in the treatment arm (combined with iota-carrageenan) - results of individual treatments may vary, trial NCT04701710.</p>	<p>continuity correction due to zero events (with reciprocal of the contrasting arm), moderate/severe COVID-19.</p>
	<p>risk of case, 84.0% lower, RR 0.16, $p = 0.004$, treatment 4 of 117 (3.4%), control 25 of 117 (21.4%), NNT 5.6, adjusted per study, odds ratio converted to relative risk, all cases, primary outcome.</p>
<p>[Hellwig], 11/28/2020, retrospective, ecological study, multiple countries, multiple regions, peer-reviewed, 2 authors, dosage 200µg/kg, dose varied, typically 150-200µg/kg, excluded in exclusion analyses: not a typical trial, analysis of African countries that used or did not use ivermectin prophylaxis for parasitic infections.</p>	<p>risk of case, 78.0% lower, RR 0.22, $p < 0.02$, African countries, PCTI vs. no PCT, relative cases per capita.</p>
<p>[IVERCOR PREP], 12/20/2020, retrospective, Argentina, South America, preprint, 1 author, dosage 12mg weekly, excluded in exclusion analyses: minimal details provided.</p>	<p>risk of case, 73.4% lower, RR 0.27, $p < 0.001$, treatment 13 of 389 (3.3%), control 61 of 486 (12.6%), NNT 11.</p>
<p>[Kerr], 12/11/2021, retrospective, propensity score matching, Brazil, South America, peer-reviewed, 9 authors, study period July 2020 - December 2020, dosage 200µg/kg days 1, 2, 16, 17, 0.2mg/kg/day for 2 days every 15 days.</p>	<p>risk of death, 70.0% lower, RR 0.30, $p < 0.001$, treatment 25 of 3,034 (0.8%), control 79 of 3,034 (2.6%), NNT 56, adjusted per study, multivariate linear regression, propensity score matching.</p>
	<p>risk of hospitalization, 67.0% lower, RR 0.33, $p < 0.001$, treatment 44 of 3,034 (1.5%), control 99 of 3,034 (3.3%), adjusted per study, multivariate linear regression, propensity score matching.</p>
	<p>risk of case, 44.5% lower, RR 0.56, $p < 0.001$, treatment 4,197 of 113,845 (3.7%), control 3,034 of 45,716 (6.6%), NNT 34.</p>
<p>[Mondal], 5/31/2021, retrospective, India, South Asia, peer-reviewed, 11 authors, dosage not specified.</p>	<p>risk of symptomatic case, 87.9% lower, RR 0.12, $p = 0.006$, treatment 128, control 1,342, adjusted per study, odds ratio converted to relative risk, control prevalence approximated with overall prevalence, multivariable, primary outcome.</p>
<p>[Morgenstern], 4/16/2021, retrospective, propensity score matching, Dominican Republic, Caribbean, peer-reviewed, 16</p>	<p>risk of hospitalization, 80.0% lower, RR 0.20, $p = 0.50$, treatment 0 of 271 (0.0%), control 2 of 271 (0.7%), NNT 136, relative risk is not 0 because of</p>

authors, dosage 200µg/kg weekly, trial NCT04832945.	continuity correction due to zero events (with reciprocal of the contrasting arm), PSM.
	risk of case, 74.0% lower, RR 0.26, $p = 0.008$, treatment 5 of 271 (1.8%), control 18 of 271 (6.6%), NNT 21, adjusted per study, PSM, multivariate Cox regression, primary outcome.
[Samajdar] , 11/17/2021, retrospective, India, South Asia, peer-reviewed, 9 authors, study period 1 September, 2020 - 31 December, 2020, dosage not specified, excluded in exclusion analyses: minimal details provided, unadjusted results with no group details, results may be significantly affected by survey bias.	risk of case, 79.8% lower, RR 0.20, $p < 0.001$, treatment 12 of 164 (7.3%), control 29 of 81 (35.8%), NNT 3.5, odds ratio converted to relative risk, physician survey.
	risk of case, 48.6% lower, RR 0.51, $p = 0.03$, treatment 11 of 109 (10.1%), control 39 of 200 (19.5%), NNT 11, odds ratio converted to relative risk, combined ivermectin or HCQ in community.
[Seet] , 4/14/2021, Cluster Randomized Controlled Trial, Singapore, Asia, peer-reviewed, 15 authors, dosage 12mg single dose, 200µg/kg, maximum 12mg, this trial compares with another treatment - results may be better when compared to placebo, trial NCT04446104.	risk of symptomatic case, 49.8% lower, RR 0.50, $p < 0.001$, treatment 32 of 617 (5.2%), control 64 of 619 (10.3%), NNT 19.
	risk of case, 5.8% lower, RR 0.94, $p = 0.61$, treatment 398 of 617 (64.5%), control 433 of 619 (70.0%), NNT 18, adjusted per study, odds ratio converted to relative risk, model 6, primary outcome.
[Shouman] , 8/28/2020, Randomized Controlled Trial, Egypt, Africa, peer-reviewed, 8 authors, dosage 18mg days 1, 3, dose varies depending on weight - 40-60kg: 15mg, 60-80kg: 18mg, >80kg: 24mg, trial NCT04422561.	risk of symptomatic case, 91.3% lower, RR 0.09, $p < 0.001$, treatment 15 of 203 (7.4%), control 59 of 101 (58.4%), NNT 2.0, adjusted per study, multivariate, primary outcome.
	risk of severe case, 92.9% lower, RR 0.07, $p = 0.002$, treatment 1 of 203 (0.5%), control 7 of 101 (6.9%), NNT 16, unadjusted.
[Tanioka] , 3/26/2021, retrospective, ecological study, multiple countries, multiple regions, preprint, 3 authors, dosage 200µg/kg, dose varied, typically 150-200µg/kg, excluded in exclusion analyses: not a typical trial, analysis of African countries that used or did not use ivermectin prophylaxis for parasitic infections.	risk of death, 88.2% lower, RR 0.12, $p = 0.002$, relative mean mortality per million.

Supplementary Data

Supplementary Data

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